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SACROCOCCYGEAL TUMORS

ADENOCARCINOMA OF A CYSTIC CONGENITAL EMBRYONAL REMNANT

E. N. BALLANTYNE, M.D.

HAMILTON, CANADA

The purpose of this paper is to introduce briefly the subject of congenital sacrococcygeal tumors, and to report a case of carcinoma that appears to have arisen from remnants of postanal intestine.

The general heading "sacrococcygeal tumors" includes a great variety, from simple fibromas and lipomas at one extreme to parasitic fetuses at the other. Dermoid cysts, teratomas and teratoid tumors are included, as well as simpler tumors, both solid and cystic.[1] The one feature common to practically all tumors that occur in this region is their congenital origin. Some occupy the anterior [2] and some the posterior [3] surface of the sacrum. In other cases, the main bulk of the tumor is slung under the coccyx, while portions of it lie both anterior and posterior to the sacrum.[4] Some of these tumors are derived from embryonal structures that normally undergo more or less complete obliteration.[5] Some of these show one type of tissue only, such as tissue of the nervous system or of the intestinal tract, while "others are complex, difficult of interpretation, and seem to involve more than one embryonal structure" (Ewing [1c]). The latter are referred to as teratoid tumors,[1] thus distinguishing them from teratoma, which contains structures or tissues that cannot be derived from local embryonal structures.

From the Pathological Laboratory, St. Joseph's Hospital.

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1. (*a*) Borst, Max: Centralbl. f. allg. Path. u. path. Anat. **9**:449, 1898. (*b*) Bland-Sutton, John: Tumors Innocent and Malignant, London, Cassell & Co., Ltd., 1922, p. 490. (*c*) Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1928, p. 1033.

2. Hundling, H. W.: Surg., Gynec. & Obst. **38**:518, 1924. Borst.[1a] Bland-Sutton.[1b]

3. Mallory, F. B.: J. M. Research **131**:113, 1904-1905. Cutler, G. D.: Surg., Gynec. & Obst. **37**:779, 1923. von Bergmann, E.: Berl. klin. Wchnschr. **21**:761, 1884. Borst.[1a] Bland-Sutton.[1b]

4. Freyer, M.: Virchows Arch. f. path. Anat. **58**:509, 1873. Jastreboff, N.: ibid. **99**:500, 1885. Simpson, J. K.: J. A. M. A. **84**:139, 1925.

5. (*a*) Mallory, F. B.: Am. J. M. Sc. **103**:263, 1892. (*b*) Hermann, C., and Tourneux, F., quoted by Mallory, Borst [1a], Hundling [2] and others. Borst [1a] Bland-Sutton.[1b] Ewing.[1c] Hundling.[2]

Sacrococcygeal tumors are frequently noted at birth, but sometimes escape notice until adult life. A relatively small proportion appear to become malignant.[6] The embryonal structures from which they may be derived include remnants of neural tube, which may be present anywhere from the lower end of the sacral canal to the tip of the coccyx,[7] neurenteric canal and postanal intestine,[8] remnants of which, when present, are usually situated on the anterior surface of the sacrum, possibly the supernumerary coccygeal vertebrae normally present in the early stages of the embryo[9] and notochord.[10]

Possibly the first recorded congenital sacrococcygeal tumor was that described by Peu, a French obstetrician of the seventeenth century (Hennig[10b]). Hamant, Cornil and Mosinger[6h] collected three hundred cases of sacrococcygeal tumors in the literature up to 1929. Most of the sacrococcygeal tumors discovered at birth or during infancy are teratomas or teratoid tumors. They are frequently large enough to cause dystocia. Speaking of teratoid tumors, Ewing[1c] said, "One-third of the subjects are born dead, and 90 per cent. of the others die in the first few days." Duncan[11] referred to a series of collected cases of congenital sacral tumors showing 50 per cent mortality and 50 per cent recovery following operation during the first year of life, and approximately 78 per cent complete recovery, 14 per cent partial recovery and 7 per cent mortality following operation after the first year of life. One of the component tissues of a teratoma or a teratoid tumor may become malignant during infancy.[12] In some cases in which malignancy had apparently not been suspected, recurrence with metastases has followed removal (Hinterstoisser's case, cited by Parin[6a]).

Sacrococcygeal tumors discovered later in life are usually less complicated. They include dermoids, simpler cystic tumors lined with squamous or columnar epithelium, gliomas, ependymal cell tumors and

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6. (*a*) Parin, reviewed by Galletly, A.: Proc. Roy. Soc. Med. **17**:105 (pt. 3) 1923-1924. (*b*) Stewart, J. D.; Alter, N. M., and Craig, J. D.: Surg., Gynec. & Obst. **50**:85, 1930. (*c*) Kraske, P.: Samml. klin. Vortr., 1897, nos. 183 and 184. (*d*) Rostock, P.: Virchows Arch. f. path. Anat. **267**:352, 1928. (*e*) Heusner, R.: Centralbl. f. allg. Path. u. path. Anat. **24**:1025, 1913. (*f*) Moersch, F. P.: M. Clin. North America **10**:715, 1926. (*g*) Pringle, S.: Lancet **1**:1643, 1907. (*h*) Hamant, A.; Cornil, L., and Mosinger, M.: Ann. d'anat. path. **6**:1224, 1929.

7. Mallory.[5a] Hermann and Tourneaux.[5b]

8. Peyron, A.: Bull. Assoc. franç. p. l'étude du cancer **17**:613, 1928; reviewed by Dukes, C. E.: Cancer Rev. **5**:129, 1930. Borst.[1a] Bland-Sutton.[1b] Ewing.[1c]

9. Keith, A.: Human Embryology and Morphology, London, Edward Arnold & Co., 1923, p. 65. Borst.[1a]

10. (*a*) Pandalia, K. G.; Forsyth, W. L., and Stewart, M. J.: J. Path. & Bact. **27**:139, 1924. (*b*) Hennig, L.: Beitr. z. path. Anat. u. z. allg. Path. **28**: 593, 1900. Ewing.[1c] Moersch.[6f] Hamant et al.[6h]

11. Duncan, H. A.: M. J. & Rec. (supp.) **120**:108, 1924.

12. Parin.[6a] Stewart et al.[6b]

chordomas. Galletly [13] held that all sacrococcygeal tumors discovered at birth are teratomas, while those not discovered until puberty or later are derived from embryonal remnants (dermoids excepted). There appear to be exceptions to the rule that sacrococcygeal tumors discovered at birth are teratomas or teratoid tumors (case of Fletcher and Waring,[14] cited under "Comment"). On the other hand, a complicated teratoid tumor may occasionally be found in an adult beyond middle life, and such a tumor may become malignant (Czerny's case, cited by Parin [6a]). Discovery in adults is made by accident or as the result of the onset of the symptoms due to the assumption of growth (sometimes malignant growth) by a previously resting structure or tissue. Frequently the symptoms consist of "sciatic pains." [15] In Moersch's [6f] series of presacral tumors, 83 per cent could be felt by rectum, and 37 per cent showed roentgenographic evidence of destruction of bone in the sacral region. Malignant sacrococcygeal tumors in adults have been classified as ependymal cell tumors ("carcinomas"), chordomas, sarcomas, carcinomas of postanal intestine and carcinomas of doubtful origin. Malignancy may supervene in dermoids. Gaffa collected a number of such cases (Duncan [11]).

REPORT OF A CASE

History.—A married woman, age 38, the mother of three children, was admitted to St. Joseph's Hospital, on March 7, 1930, complaining of continual pain, or rather discomfort, in the left buttock ("cannot sit down"). On standing, she felt a weight and a pulling sensation. Nearly two years before, she first noticed that she could not sit for any length of time with comfort. About fifteen months before, distress became more noticeable. At that time a doctor examined her, but found no cause for the distress. About a month before admission, she was examined by her physician, who discovered and tapped a cyst at the lower end of the spine, from which he removed about a pint (473 cc.) of fluid.

The family history is not relevant. The only points in the past and personal history that have any bearing on the case are that the first confinement was difficult, and that the present complaint started not long after the birth of the last child.[16]

Examination and Operation.—Physical examination showed nothing abnormal, except puffiness over the sacrum, due to a cyst situated in that region. A roentgenogram (fig. 1) showed a deficiency involving the lower end of the sacrum and the coccyx. The preoperative diagnosis was: dermoid of the coccygeal region.

At operation, March 7, a cyst was found, which occupied a deficiency in the sacrum and coccyx, and lay against the wall of the rectum anteriorly and immediately beneath the skin posteriorly. It was not adherent to the skin, but was adherent to the posterior wall of the rectum at one point. The cyst was drained of about a

13. Galletly, A.: Proc. Roy. Soc. Med. **17**:105 (pt. 3) 1923-1924.

14. Fletcher, H. M., and Waring, H. J.: Tr. Path. Soc. London, 1900, p. 226.

15. Hundling.[2] Moersch.[6f]

16. Hundling [2] also reported a case of presacral carcinoma in which there was a history of difficult labor with the patient's first child.

pint (473 cc.) of thick material that "looked somewhat like pus." The sac was excised and the cavity packed with gauze.

The gross specimen consisted of a number of thin sheets resembling fibrous tissue, one surface being brownish pink and finely granular.

Histology of Tumor.—Figure 2 shows the cryptlike or intestinal glandlike arrangement of the tissue lining the inner surface of the cyst. It also shows the columnar type of epithelium, which resembled intestinal epithelium. In places

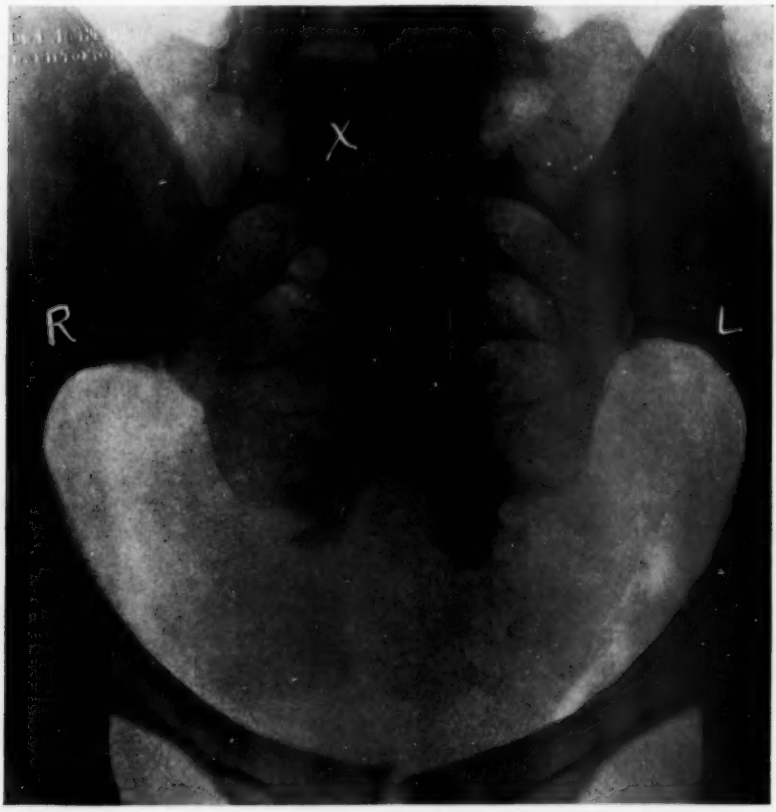

Fig. 1.—Roentgenogram showing deficiency in the sacrum and coccyx. It is not certain whether the vertebra marked *x* is a fused last lumbar vertebra or the first sacral vertebra. If it is a fused last lumbar vertebra, there are three sacral vertebrae and the deficiency; but if it is counted as the first sacral vertebra, there are four sacral vertebrae and the deficiency. Dr. L. R. Hess reported the deficiency as erosion. Both congenital deficiency and erosion occur with sacrococcygeal tumors. The sacrum has been found rudimentary in congenital tumors on the ventral surface of the sacrum by Pannwitz (quoted by Borst [1a]), Stewart, Alter and Craig,[6b] Pandalia, Forsyth and Stewart [10a] and others. On the other hand, Hundling [2] and others referred to the presence of erosion in such cases. In the present case, the gradual onset of symptoms of pain and discomfort on sitting was probably associated with the progress of the erosive process. The pain was on the left, the side with the long projecting remnant of bone. It is impossible to determine whether a congenital deformity did or did not exist previous to the onset of erosion.

where the epithelium covered the rounded surface between cryptlike depressions, the cells were elongated and assumed a rather fan-shaped arrangement, such as is frequently seen on the rounded surface between crypts in sections of appendix. The stroma contained plasma cells, lymphocytes and eosinophils in places. A higher magnification of the outlined area is shown in figure 3.

Figure 3 is shown particularly for the sake of the goblet cells that were present. By direct observation of this field under the microscope, eight goblet cells could be seen. Only five are distinctly within the focal plane in figure 3. The one that is sharply in focus shows its nucleus. To the left of this goblet cell are two mitotic figures. Basic-staining material like mucus was observed in the crypts or lumina of the glands in some of the sections.

Fig. 2.—Tissue forming part of the lining of the cyst. It shows resemblance to intestinal glands and stroma. A higher magnification of the area encircled is shown in figure 3.

In the section from which figure 4 is taken there was at one point a sudden transition from tissue having the comparatively orderly arrangement seen in figures 2 and 3 to frankly carcinomatous tissue. This reminded one very much of the sudden transition that is so frequently seen from normal intestinal mucosa to adenocarcinoma, except that the glandular character of the carcinoma in the present instance was much less obvious and the histologic evidence of malignancy was much greater. Lumina were minute and difficult of detection. In parts of this microscopic section, however, and also in other sections, the adenomatous character of the malignant tissue was evident. This photomicrographic field was chosen primarily to demonstrate the histologically malignant characteristics of the tissue. Other sections showed widespread infiltration of the fibrous wall of the cyst by tissue of this frankly carcinomatous type, usually with a distinct attempt at a gland-like arrangement. There were some extremely large cells, with highly hyperchromatic nuclei.

Fig. 3.—Higher magnification of the area outlined in figure 2, showing goblet cells among the columnar epithelial cells of two glands.

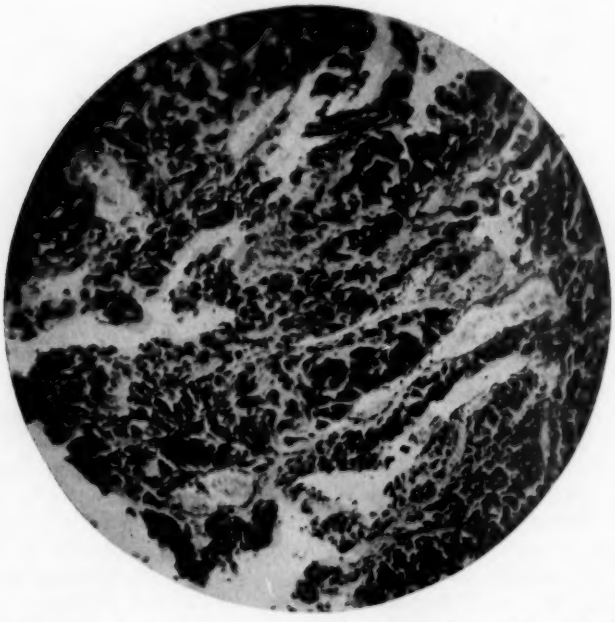

Fig. 4.—Adenocarcinomatous tissue forming part of the lining of the cyst.

A tubular structure that was present in one of the sections was lined with cuboidal epithelium, and was about 0.75 mm. in its greatest diameter. One and one-half millimeters to the right of this in the section was a strip of stratified squamous epithelium 1.5 mm. by 0.1 mm., showing that this tubular structure lay not far beneath the skin. Slightly farther to the right and below in this same section were scattered, invading glandlike structures and part of the epithelial lining of the cyst. This tubular structure was almost an exact duplication of one of the tubular structures depicted by Mallory [5a] in his article describing remnants of medullary tube found in fetuses. I believe this to have been a persistent remnant of medullary tube, which communicated with the subdural space of the spinal canal. The subsequent history of the case supports this contention.

Course in Hospital.—At 3:30 p. m. on the day of operation, the patient complained of headache, and at 8:30 p. m. when the dressing was changed it was said to be saturated with serous discharge. On the next day, the patient complained of both frontal and occipital headache, which was described as terrible. Nausea, vomiting and free perspiration occurred. Dressings were again saturated with serous discharge. Headache became a daily feature, practically continuous, except when temporarily relieved by medication. The presence of watery discharge was noted whenever the dressing was changed. The temperature began to be elevated, at first to 99 F., then to 101 F. It was realized that cerebrospinal fluid was leaking from the incision. To help prevent excessive loss of spinal fluid, the foot of the bed was elevated.

The patient's condition gradually improved; the discharge of spinal fluid and the headache gradually became less. By the end of the second month after operation, there was little if any discharge of spinal fluid, and the patient usually made no complaint of headache. She began to sit up in a chair for a part of each day, and was dismissed from the hospital about the beginning of the third month after operation.

Course After Leaving Hospital.—During the fourth month after operation, enlarged glands were noted in the groin. It was considered that these were metastases.

During the fifth month after operation, the patient began to have high fever and complained of pain at the site of operation. On rectal examination, a bulging mass could be felt behind the rectum. There was a small opening through the old incision that had never entirely closed. Through this opening, a quantity of semi-necrotic tissue was curetted away, and the patient had relief while there was free drainage. Two or three weeks later radium was inserted. At this time "malignant granulations" were present about the wound. For about a month the patient felt better.

During the sixth month after operation, the patient began to cough, and about two weeks later there were signs of consolidation in the right lung. These pulmonary symptoms were interpreted as signs of metastases in the lung. About this time, also, the patient began to have recurrent vomiting.

About the end of the seventh month after operation, a mass was felt in the sigmoid region; the stools became very small and ribbon-like, and visible peristalsis was noted. The patient lost weight and died about eight months after operation. A necropsy was not obtained.

COMMENT

Middledorpf [17] was the first to attribute a congenital sacrococcygeal tumor to postanal intestine. His was the first reported sacrococcygeal

17. Middledorpf, K.: Virchows Arch. f. path. Anat. **101**:37, 1885.

tumor to contain intestine only. Those previously reported by Freyer [4] and others contained connective tissue, bone, cartilage or muscle in addition to intestine. The tumor in Middledorpf's case, that of a girl 1 year old, was successfully removed by Kraske. It consisted of small loops of intestine lying embedded in fat behind the rectum and adherent to the latter in an area about the size of a small finger nail. In the latter respect, it resembled the case that I have now reported. Bland-Sutton [1b] stated that he had considered postanal intestine the source of intestine-containing tumors in this region even before Middledorpf reported his case. Borst [1a] considered that tumors situated on the anterior surface of the sacrum and coccyx containing intestine-like structures were derived from postanal intestine, but he found no recorded case of carcinoma that might have arisen from this source. Carless [18] said that congenital adenoma of postanal intestine is innocent. Ewing [1c] agreed that a number of tumors in this region are derived from postanal intestine, but did not refer to the possibility of malignancy in this connection.

Hundling [2] reported two ventral tumors of the sacrum, which were carcinomatous. One was diagnosed as colloid carcinoma; the other as adenocarcinoma. The epithelium in the latter was cuboidal. In the reports of these two cases, no opinion is expressed as to their origin, but in the general discussion postanal intestine and remnants of neural tube ("ependymal cells") are referred to as possible sources.

Fletcher and Waring [14] reported an adenocarcinoma which they considered was derived from postanal intestine. This occurred in a boy, 2 years old, and was made up of a firm portion consisting of cysts lined with columnar epithelium, embedded in fibrous tissue, and a soft adenocarcinomatous portion. The tumor was removed, but death followed recurrence. At necropsy, tumor tissue was found enveloping without actually invading the rectum.[19] The rectum was narrowed at the pelvic brim, and the intestine above it was distended. There were metastases in the iliac and lumbar glands. The clinical history in the case that I have reported suggests a somewhat similar mode of extension.

Kraske [6e] observed two cases that he considered to be cases of carcinoma of postanal intestine, based on the postrectal position, relation to surrounding structures and microscopic appearance. Rostock [6d] quoted Galletly [13] as having reported another case, but examination of the original report does not substantiate Rostock's statement. Galletly con-

18. Carless, A., in Rose and Carless: Text-Book of Surgery, Toronto, J. F. Hartz Company, 1924, p. 809.

19. Kraske [6c] stressed this noninvasion of the rectum in carcinoma of postanal intestine.

sidered his case to be one of tumor of the neurenteric canal, but made no suggestion that it was malignant. It is true that there were two recurrences of this tumor at intervals of years after removal, but this was apparently due to incomplete removal rather than to malignancy. Rostock also reported a case of his own, an adenocarcinoma, which, he concluded, was from postanal intestine. Beyond saying that it was "an infiltrating epithelial tumor of glandular structure," he gave no histologic details to establish his claim. Therefore, the type and origin of this adenocarcinoma remain in doubt. This was also the opinion of Dukes,[20] expressed in a review of Rostock's report.

It seems probable that the intestinal portions of some of the more complex congenital sacrococcygeal tumors have arisen from postanal intestine. This is the view of Nasse,[21] Borst,[1a] Bland-Sutton [1b] and Ewing.[1c] Stewart, Alter and Craig [6b] collected four cases of what they termed sacrococcygeal teratoma with malignant degeneration in childhood, and reported one case of their own. In only one of these cases did the evidence point strongly to an origin of the malignant tissue from postanal intestine, and there appears to have been no evidence to warrant classifying the tumor as a teratoma, since only epithelium and fibrous tissue were found in it. This was the case of Fletcher and Waring,[14] which has been discussed.

SUMMARY

It seems to me that the evidence in the case now reported is sufficient to justify the diagnosis of adenocarcinoma of postanal intestine. The criteria required by Peyron [8] in order to establish the diagnosis of postanal intestine cyst are present in this case, viz., columnar epithelium, goblet cells, presence in the lumina of material staining like mucus and absence of muscle or serous coat to the cyst. Peyron's opinion is based on many years of study of abnormalities of animals and of dissection of human embryos. Although there is evidence that the medullary tube was persistent below the exit of the sacral canal, yet this took no part in the formation of the tumor, the tumor being purely one of postanal intestine. There was no evidence of gliomatous tissue in this case. Neither was anything found to suggest a teratoid nature. Although many microscopic sections were made, no tissues were found other than those described. Only four other cases have been reported as carcinoma of the postanal intestine. The evidence in one of these cases is scant and unconvincing. In a few other cases, an origin of carcinoma from postanal intestine appears to have been suggested indirectly.

20. Dukes, C. E.: Cancer Rev. **3**:421, 1928.
21. Quoted by Borst [1a] and Ewing.[1c]

BANDS AND RIDGES IN THE PULMONARY ARTERY

THEIR RELATION TO AYERZA'S DISEASE

O. SAPHIR, M.D.
CHICAGO

Cordlike structures within the vascular system constitute a very rare finding. Occasionally, they are found in the right auricle, forming a netlike structure. If present in the aorta and pulmonary arteries, they usually are located just above the area of the valves. In these locations they are, as a rule, regarded as congenital anomalies and explained on the basis of an abnormal developmental course of the septum within the truncus arteriosus. Bands in branches of the pulmonary artery, however, are, as far as could be determined, described only by Möller [1] and by Steinberg.[2] The results of a study of bands and ridges in the pulmonary arteries are now reported. A congenital anomaly as an underlying cause of these formations could be ruled out.

LITERATURE

The literature on this subject is scant. Posselt [3] described a band in the pulmonary artery extending from the right cusp of the pulmonary valve to the intima of the pulmonary artery. In another case he mentioned a band in a segment of the pulmonary artery at a distance of about 1 cm. from the pulmonary valve. This band was 3 cm. long and had its origin and insertion in the intima of the artery. Its midportion crossed part of the lumen. Even though the bands were present in two old people, the author believed that they occurred on the basis of a congenital anomaly. Zahn [4] found a peculiar netlike structure in the left pulmonary artery of a 52 year old man who had died of pulmonary emboli. This net consisted of strings and thin membranes, which were attached to the intima, and which crossed parts of the lumen of the

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From the departments of pathology of the Nelson Morris Institute of the Michael Reese Hospital, and of the University of Illinois Medical School.

1. Möller, P.: Beitr. z. path. Anat. u. z. allg. Path. **71**:27, 1923.
2. Steinberg, U.: Beitr. z. path. Anat. u. z. allg. Path. **82**:307 and 443, 1929.
3. Posselt, A.: Ergebn. d. allg. Path. u. path. Anat. **13**:298, 1909.
4. Zahn, F. W.: Virchows Arch. f. Path. **115**:47, 1889.

pulmonary artery. Zahn did not believe that these structures were the result of organized thrombi, but ventured the opinion that they represented a congenital anomaly. Röhrle [5] described a cordlike structure in the aorta just above the aortic valve in a 2 weeks old child. He also mentioned the museum specimens of Nickiforoff and of Rosenberg, which revealed bands in a similar location. Chiari [6] and also Mönckeberg [7] described netlike structures in the right auricle. They were regarded as remnants of the valvula venosa dextra and of the septum spurium. Mönckeberg, however, remarked that in Rosenberg's specimen the band might represent excessive fenestration of the aortic valve. Poscharissky [8] described a band just above the pulmonary valve, and expressed the belief that the band originally was a part of the pulmonary valve, which had been torn away, probably because of excessive fenestration. It is interesting to note that Mönckeberg stated that such "anomalies" occasionally might be produced by a faulty opening of blood vessels. Artefacts therefore must be ruled out in considering the etiology of bands in vessels. Schober [9] also explained by excessive fenestration of the cusps a cordlike structure found just above the aortic valve in a 4 months old child. Lucksch [10] described a thin cord running across the lumen of the ascending aorta in a man aged 76. Arteriosclerotic lesions were absent. The cause of this formation was explained by an abnormal course of the septum in the truncus arteriosus. Möller [1] found bands in the pulmonary artery in four cases. Because of the fact that in three instances iron-containing pigment was found in the bands, he thought that the bands represented organized thrombi. A detailed histologic description, however, is missing. Steinberg [2] observed several bands connecting thickened areas of the intima of the pulmonary arteries. He noted in detail the changes of the pulmonary arteries histologically, but did not mention the finer structures of the bands. Verse [11] described bandlike structures in the splenic vein in a case of cavernous transformation of the periportal tissue with old thrombosis of the portal vein. These structures were regarded as newly formed blood vessels with marked intimal proliferation which had led to almost complete obliteration of their lumina.

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5. Röhrle, F.: Deutsche med. Wchnschr. **22**:270, 1896.
6. Chiari, H.: Beitr. z. path. Anat. u. z. allg. Path. **22**:1, 1897.
7. Mönckeberg, J. G.: Deutsche med. Wchnschr. **33**:1243, 1907; Die Missbildungen des Herzens, in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, J. Springer, 1924.
8. Poscharissky, J. G.: Beitr. z. path. Anat. u. z. allg. Path. **35**:521, 1904.
9. Schober, F., in Studien zur Pathologie der Entwicklung, Jena, 1920, vol. 2, p. 527.
10. Lucksch, F.: Centralbl. f. allg. Path. u. path. Anat. **23**:626, 1912.
11. Verse, M.: Beitr. z. path. Anat. u. z. allg. Path. **48**:526, 1910.

The study here presented is based on examination of bands in the pulmonary artery in one case and of ridges in the pulmonary artery in another case. Both structures were encountered in the course of postmortem examinations.

DESCRIPTION OF CASES

CASE 1.—The clinical diagnosis in the case of a man, 60 years old, was: generalized arteriosclerosis, arterial hypertension and cardiac decompensation. There was no evidence of pulmonary arteriosclerosis, such as marked dyspnea or cyanosis. At postmortem examination, the heart weighed 850 Gm., was hypertrophic and dilated, and contained mural thrombi in the right auricle. There were diffuse

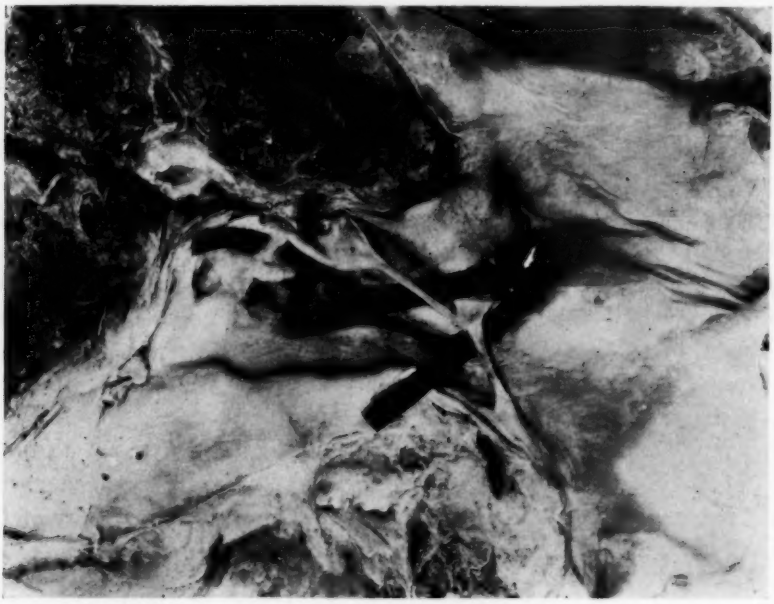

Fig. 1 (case 1).—Pulmonary artery opened. Note bands.

arteriosclerosis, coronary sclerosis with myocardial fibrosis, bilateral nephrosclerosis of the arteriolar variety and edema of both lower extremities. The lungs were distended and emphysematous. When the main branches of the pulmonary arteries were opened, a number of bands were noted on both sides. They were covered with intima and were yellowish and smooth. Some were flat and thick, others thin and delicate. The former, as a rule, were short, measured less than the diameter of the pulmonary artery, and crossed transversely a small portion of the lumen. The latter were much longer and crossed almost the entire lumen. The bands measured from 3 to 10 mm. in length. They arose from and had insertion in portions of thickened intima. They were not present in the common pulmonary artery, but were found in the main right and main left branch and also in the smaller distributions. On cross-section, the bands were light gray and showed a few darker red spots. In several instances emboli were found, caught apparently between the

intima of the pulmonary artery and the bands. There were many areas of intimal thickening in the pulmonary arteries, yellow areas of fatty degeneration, and some hyalinization. No atheromatous ulcers were noted.

Portions of the pulmonary artery with the bands were hardened in 10 per cent formaldehyde and embedded in paraffin. Serial sections were cut from one of the bands. Every third section was stained with hematoxylin-eosin, with a combination of iron-hematoxylin and orcein, and according to the van Gieson method. From some bands and portions of thickened intima of the pulmonary arteries, frozen sections were cut and stained for fat with sudan III.

Sections taken from the pulmonary artery close to the insertion of the band revealed marked intimal proliferation, with connective tissue formation and hyalini-

Fig. 2.—Structures resembling blood sinuses. Note fibrous cord lined by endothelial cells; iron-hematoxylin-eosin preparation; × 100.

zation. Stained for fat, these portions revealed a moderate number of fat globules. Only a few spindle-shaped cells and, occasionally, lymphocytes were noted. There were small blood vessels in the intima. The media contained thick elastic fibers. No foci of lymphocytic infiltration could be demonstrated in the adventitia.

Sections taken from the points of insertion of the bands into the intima of the pulmonary artery showed much more connective tissue, which formed knoblike projections into the lumen of the artery. In some portions, the fibers seemed very loose and spread by an edema-like material. Several stellate-shaped cells with processes were found in this region. There were many small, newly formed blood vessels and a moderate number of lymphocytes and endothelial cells, some of which contained brown, granular pigment. In one area within the proliferated intima but close to the media, there was a large amount of fibrin, with many blood platelets,

red blood corpuscles, and clumps of dark brown, apparently hemosiderotic pigment. Lymphocytes and endothelial cells were found at the periphery of this region. A capsule of connective tissue separated this area from the surrounding intima and media. Serial sections revealed that these structures were present where the band was attached to the wall of the pulmonary artery, but that they did not extend into the neighboring intima. The media in this region revealed thick elastic and muscle fibers; but no cellular infiltrations were found. The adventitia showed no changes.

Sections taken from the bands themselves showed many connective tissue cells, loose fibers and small-sized blood vessels. There were many endothelial cells, some of which were filled with pigment granules, lymphocytes and, occasionally, poly-

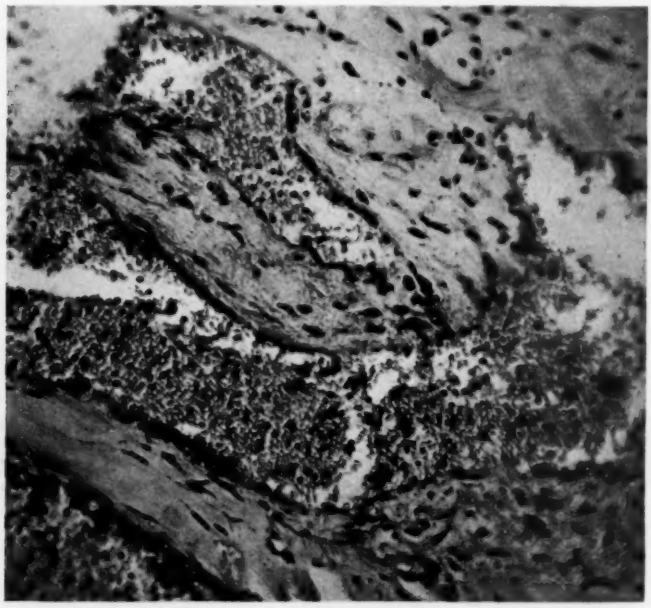

Fig. 3.—Field similar to that in figure 2; iron-hematoxylin-eosin preparation; × 300.

morphonuclear leukocytes. Some portions of the band showed dense masses of pigment granules, strips of fibrin with many red blood corpuscles, masses of platelets, and more connective tissue than in the end-portions of the bands. Some sections revealed dense connective tissue fibers with hyalinization and only a few spindle-shaped cells. Many sections revealed large encapsulated areas with many red blood corpuscles. From the capsule, connective tissue fibers in the form of papillae or fibrous cores lined by endothelial cells extended into the hemorrhagic zone. In some portions, these fibrous cores had almost entirely replaced the hematoma, while in others large blood sinuses were still present, which were bound by connective tissue processes lined by endothelial cells. These formations were seen in many sections but were more pronounced in those taken from the midportions of the bands. The orcein stain showed thin elastic fibers throughout the bands.

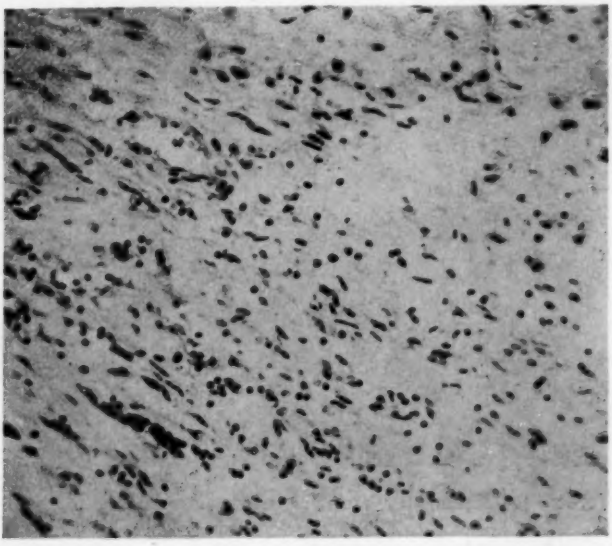

Fig. 4.—Inflammatory cells within bands; iron-hematoxylin-orcein preparation; × 200.

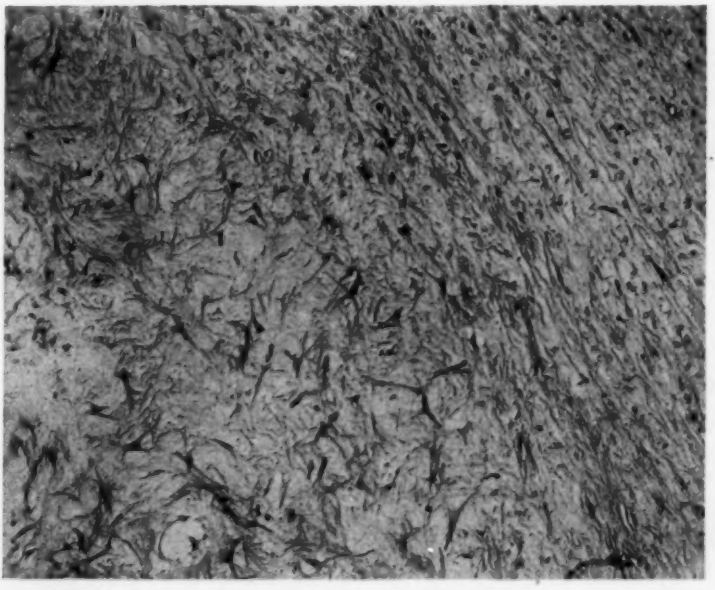

Fig. 5.—Mucoid degeneration. Note stellate-shaped cells; hematoxylin-eosin preparation; × 100.

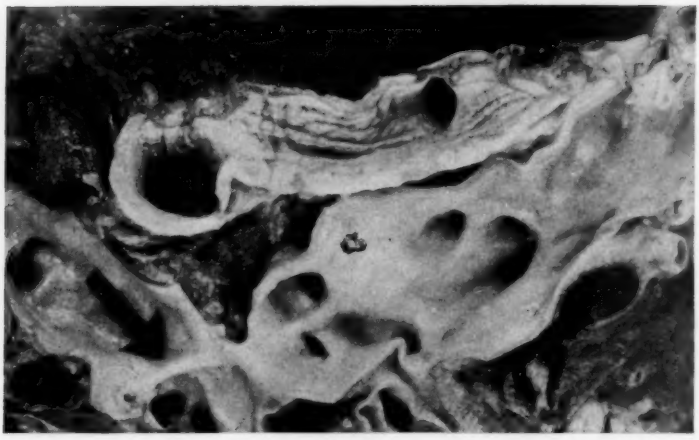

Fig. 6 (case 2).—Pulmonary artery opened. Arrow is directed toward one of ridges.

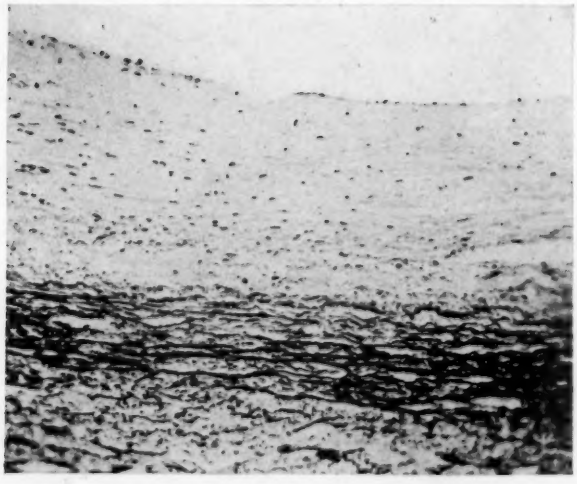

Fig. 7.—Arteriosclerosis of pulmonary artery; iron-hematoxylin-orcein preparation; × 100.

To summarize—a patient with arterial hypertension and nephrosclerosis of the arteriolar variety, who died from cardiac decompensation, showed many bandlike structures in the pulmonary arteries, in addition to arteriosclerotic plaques. Histologically, the bands consisted of young and old connective tissue, with hyalinization. There were endothelial cells and lymphocytes present, also many red blood cells and pigmented areas. Newly formed blood vessels and blood sinuses were found throughout. The bands themselves were lined by intimal lining cells. In short, the bands represented organized and still organizing thrombi.

CASE 2.—The clinical diagnosis in the case of a 49 year old man was cardiac decompensation with diffuse arteriosclerosis. The patient did not show marked dyspnea or cyanosis, and there was no evidence, clinically, of pulmonary arteriosclerosis.

The autopsy revealed diffuse arteriosclerosis, nephrosclerosis of the arteriolar variety, and emphysema of the lungs. The heart was hypertrophic and dilated, weighing 650 Gm. The pulmonary artery appeared somewhat wider than normal. The common pulmonary artery and its branches showed many arteriosclerotic plaques. In some of the branches, several yellow ridgelike elevations of the intima were found, extending perpendicular to the long axis of the vessels. The ridges were sharp and well circumscribed, measuring up to 10 mm. in length and about 2 mm. in width. They were found between orifices of branches of the pulmonary arteries but were not present at the branching points. None of the ridges were undermined. There was no evidence of formation of bands.

On microscopic examination, these ridges showed a moderate connective tissue stroma with a few red blood cells dispersed throughout. There was some hyalinization. Small blood vessels were present, extending from the wall of the artery into the wall of the ridges. Lymphocytes and endothelial cells were found between the connective tissue fibers. Some of the endothelial cells contained pigment granules, but these were also seen free in the tissue. Some sections still showed old fibrin with blood platelets and a few polymorphonuclear leukocytes. The ridges were covered by intimal lining cells, forming a distinct continuation of the lining cells of the surrounding intima. The pulmonary artery in the region of the ridges showed much fibrosis and hyalinization. Occasionally, fat globules were noted in frozen sections. A few small-sized blood vessels were found in the intima, some of which were obliterated. The adventitia and media showed no changes.

To summarize—in a patient who died from cardiac decompensation associated with diffuse arteriosclerosis, nephrosclerosis of the arteriolar variety and emphysema of the lungs, ridges were found in the pulmonary artery. Histologic examination showed that these ridges were organized mural thrombi covered by intimal lining cells.

COMMENT

In the first case, bands were found crossing the lumina of branches of the pulmonary arteries. The sections revealed that these bands were organized thrombi covered by intimal lining cells. The pulmonary

arteries were the seat of moderate pulmonary arteriosclerosis. It is likely that the thrombi originally were formed on roughened areas of the intima because of atherosclerotic changes in the pulmonary arteries. This question, however, will be discussed subsequently. It is possible that organization of the thrombi had started more actively in only one or two places, while the remainder of the thrombi were detached from the wall, either because of shrinkage of the thrombus or because of the systolic pressure of the blood stream. This pressure must also have molded the thrombi in such a fashion as to form the bands. There is no evidence that a congenital anomaly might have been the underlying cause for the formation of the bands in this case. The fact alone that the bands were found in branches of the pulmonary artery makes such an origin improbable.

The ridges found in the second case resembled, at the first glance, so-called spurs found in the intima of the pulmonary artery close to the orifices of the smaller branches. But while such spurs histologically show the structures of the normal wall, with possibly some plain intimal thickening, the ridges here reported proved to be organized mural thrombi covered with intimal lining cells.

The literature contains only a few references to bandlike structures in blood vessels. As was mentioned before, Möller [1] found bands in the pulmonary artery which he interpreted as results of organized emboli. He did not mention arteriosclerotic lesions in the pulmonary arteries in his cases. Because of a possible relation of thrombi and bands, respectively, to pulmonary arteriosclerosis, the literature on pulmonary arteriosclerosis was searched for a description of bands. Only Steinberg,[2] in one of his two cases of primary pulmonary arteriosclerosis, mentioned structures apparently similar to those described in this paper. As was mentioned before, however, he did not give a histologic description of the bands. Grafe [12] and also Hart [13] mentioned the finding of thrombi in pulmonary arteriosclerosis. Ljungdahl [14] stated that in most cases of arteriosclerosis of the systemic circulation there is also revealed some pulmonary arteriosclerosis. Both of the patients whose lesions are described in this paper were over 60 years of age and had marked diffuse arteriosclerosis.

A number of cases of marked pulmonary arteriosclerosis are reported in the literature as Ayerza's disease.

The question arises whether or not the cases described here may be classified as cases of Ayerza's disease with pulmonary arteriosclerosis,

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12. Grafe: München. med. Wchnschr. **70**:1352, 1923.

13. Hart, C.: Berl. klin. Wchnschr. **53**:304, 1916.

14. Ljungdahl, M.: Untersuchungen über die Arteriosklerose des kleinen Kreislaufes, Munich, J. F. Bergmann, 1915.

mural thrombi and subsequent formation of bands and ridges. Cheney [15] stated that cough, dyspnea, cyanosis and somnolence are the characteristic clinical symptoms. Edema is usually a late occurrence. The patients appear intensely cyanotic and present other signs and symptoms of a severe cardiac decompensation. The red blood corpuscle count is usually over 5,000,000 and may reach 10,000,000. In six of eight cases in which the result of the Wassermann test was recorded, according to Cheney, the reaction was positive. Both of the patients concerned in the present study were over 60 years old. Both showed hypertensive heart failure clinically, and generalized arteriosclerosis, nephrosclerosis of the arteriolar variety, emphysema and hypertrophic and dilated hearts at autopsy. The Wassermann reaction in both cases was negative. The red blood count was 4,220,000 and 4,600,000, respectively. If, as Cheney stated, Ayerza's disease signifies a primary pulmonary arteriosclerosis resulting mainly in hypertrophy of the right ventricle, the two cases reported here are not examples of Ayerza's disease. The cardiac failure may easily be explained by the nephrosclerosis and the diffuse arteriosclerosis. The right ventricular hypertrophy in both cases was the result of the emphysema. The sclerosis of the pulmonary artery, especially the bands and ridges, might have been an additional factor in causing hypertrophy of the right side of the heart. The cause of the pulmonary arteriosclerosis in cases of Ayerza's disease, is, according to Cheney, usually or probably always syphilitic. In his case, Cheney described a striking round cell infiltration of the vasa vasorum of the adventitia and loss of the elastic fibers in the media of the pulmonary arteries. In the cases described here there was no evidence of syphilis clinically, serologically or histologically.

Structures somewhat similar to the bands and ridges reported here are encountered frequently in the endocardium of the left ventricle in cases of incompetence of the aortic valve, in the form of plain endocardial thickenings, bands or endocardial pockets. Only rarely, they are found in the auricles. As was shown in a previous paper,[16] endocardial thickenings and endocardial pockets are the result of either mechanical irritation or mural endocarditis. In other words, they might signify end-stages of healed thrombi. The pressure of the blood stream secondarily often undermines the thickened areas, producing bands or, sometimes, pockets. The bands in the pulmonary arteries of the first case showed a similar origin. There was a primary thrombosis which had undergone organization. These bands, similar to those in the endocardium, were formed secondarily, apparently by the force of the systolic pressure in the pulmonary circulation.

15. Cheney, G.: Am. J. M. Sc. **174**:34, 1927.
16. Saphir, O.: Am. J. Path. **6**:733, 1930.

In the foregoing paragraphs, the term thrombus was used to designate the primary lesion in the pulmonary artery. Whether the primary lesion was really a thrombus rather than an embolus is, of course, difficult to decide, especially because of the fact that mural thrombi were found in the auricles in the first case and also recent emboli in branches of the pulmonary artery. In both cases, arteriosclerotic changes were present with hyalinization and fatty changes, but no atheromatous ulcers. It does not seem justifiable to assume that such a hypothetic ulcer, which had healed, might have formed the basis of the mural thrombus. I also should like to mention Ljungdahl's statement that atheromatous ulcers in pulmonary arteriosclerosis are extremely rare. It seems much more likely that intimal thickenings and the roughened intimal surfaces alone suffice to cause the formation of thrombi. Mönckeberg [7] also stated that in one of his two reported cases of pulmonary arteriosclerosis, mural thrombi were found on circumscribed thickened areas of the intima, but not on an atheromatous ulcer. The emboli in the pulmonary artery in the first case were recent. It is interesting to note that they had lodged between the bands and the intima, where they were firmly implanted but not organized.

SUMMARY

Multiple bandlike structures in the pulmonary arteries are described in one case, and ridgelike formations in another. These structures are the result of organized mural thrombi. It is believed that the systolic pressure in the pulmonary artery transformed the thrombi into bands. A congenital anomaly could be ruled out as the underlying cause of these structures. Pulmonary arteriosclerosis was the primary cause of the mural thrombi. There was no evidence of Ayerza's disease.

RELATION OF FIBRO-ADENOMA AND CHRONIC MASTITIS TO SEXUAL CYCLE CHANGES IN THE BREAST

HELEN INGLEBY, M.B., M.R.C.P.
PHILADELPHIA

In 1907, Hitschmann and Adler [1] described the endometrium in the different stages of the menstrual cycle, thus throwing an entirely new light on lesions of the uterus. It is known that these changes are correlated with the development and the regression of the corpus luteum. In 1922, Rosenberg [2] cut sections of breast and uterus in cases coming to autopsy and found a similar sexual cycle in the breast. Polano [3] and Sebening [4] confirmed these findings in surgical cases, but denied that postmenstrual regression is always complete.

Before considering pathologic changes it is necessary to examine the normal sexual cycle in the breast. The normal resting breast (about the middle ten days of the cycle) consists of fibrous tissue and ducts. In older women and in obese young women fat is present also. The ducts are lined by two layers of cells (often more than two are seen). The cells of the inner layer are cuboid or columnar. The nuclei are small and stain deeply. In good preparations, the dark staining may be seen to be due to a very fine, close chromatin meshwork. A nucleolus is also present. The protoplasm is scanty, so that the nuclei almost touch each other. The cell outlines are ill-defined, but toward the lumen of the ducts the epithelium presents a regular even line. The basal cells are smaller and tend to be flattened. As the time of the menstrual period approaches, the cells become larger, they divide and new ductules are formed branching out from the old ducts like twigs on a tree. The epithelial border around the lumen becomes somewhat jagged and irregular, a change similar to that seen in the glands of the premenstrual endometrium. Meanwhile the periductal fibrous tissue softens, undergoing myxomatous and hyaline degeneration so as to allow for the expansion of the ducts. The perilobular fibrous tissue is pushed to one side. In this way lobules that do not

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From the Department of Pathology of the Woman's Medical College of Pennsylvania and the Research Institute of the Lankenau Hospital.

1. Hitschmann, F., and Adler, L.: Wien. med. Wchnschr. **57**:1297, 1907.
2. Rosenberg: Frankfurt. Ztschr. f. Path. **27**:466, 1922; Virchows Arch. f. path. Anat. **262**:298, 1926.
3. Polano, O.: Ztschr. f. Geburtsh. u. Gynäk. **87**:363, 1924.
4. Sebening, W.: Arch. f. klin. Chir. **134**:464, 1925.

exist in the normal resting breast are formed by the terminal portion of a duct and its branches. The epithelial cells swell, the protoplasm is often vacuolated, and the nuclei are rounder and paler, the chromatin meshwork being spread apart by a colorless substance. Similar changes are seen in the cells of the basal layer. Secretion takes place into the ducts, which become more or less distended, the amount of proliferation as well as of secretion differing considerably in different persons. In many women, the breasts become swollen and tender at this stage. About a day or so before the onset of the menstrual flow, involution begins. The epithelium degenerates. The cells of the basement layer especially become extremely vacuolated, and cleavage takes place along this line. Toward the end of the period, the degenerated epithelium is shed into the lumen of the ducts, much as the superficial layers of the endometrium are cast off during menstruation. Under the microscope, the lobules at the postmenstrual stage have a curiously jumbled appearance. The architecture of the ductules is lost, and one sees irregularly staining, degenerated epithelial cells, often varying in size and shape, intermingled with round cells and proliferating fibrous tissue. In the late postmenstrual phase, the degenerated epithelial cells are absorbed; for a short time, clefts may be seen in the tissue where the ducts have been, but these disappear, and the breast returns to the resting condition.

The amount of new growth taking place in the breast at each sexual cycle is astonishing. Premenstrual proliferation is much more rapid than carcinomatous growth. A point to be borne in mind is that the connective tissue of the breast proliferates and degenerates in inverse ratio to the epithelium; and although it would appear that the perilobular tissue is subject to compression by the growing ducts and to expansion when the pressure is removed, yet as regards periductal tissue there seem to be true growth and degeneration. A factor that must be allowed for in any discussion of the structure of the breast is that, even in normal breasts, different parts show differences in rate of proliferation and regression, so that at any given moment the lobules are not all exactly alike. McFarland[5] emphasized this with regard to involution after lactation, and the same is true of postmenstrual involution. Under pathologic conditions, as will be seen later, these differences become more marked.

Transplants of mammary tissue show the same cyclic changes,[6] thus proving their origin in hormonal influences. The substances regulating this growth seem to be secreted by the graafian follicle and the corpus luteum of the ovary under the influence of hormone or hormones from

5. McFarland, J. J.: Surg., Gynec. & Obst. **45**:729, 1927.

6. Parkes, A. S.: Internal Secretions of the Ovary, New York, Longmans, Green & Co., 1929.

the anterior lobe of the pituitary gland. Experiments indicate that the corpus luteum is responsible for hyperplasia of the parenchymatous tissue of the breast. The following is a summary of recent work in this direction:[7]

1. Many workers have induced hypertrophy of the mammae in normal and in ovariectomized animals, in normal and in castrated male guinea-pigs, in young male dogs and in castrated monkeys by injecting estrin. This hypertrophy, no matter how prolonged the injections of estrin, has never been equal to the development of the breasts in pseudopregnancy or pregnancy, and is probably comparable to the hypertrophy observed at each estrual cycle. The conclusion of most observers is that estrin cannot cause complete development of the mammary gland.

2. The development of the mammary gland in pseudopregnancy and pregnancy seems to be definitely associated with the corpus luteum, for the following reasons:

(*a*) In animals with a short corpus luteum stage in the ovarian cycle there is hardly any change in the breast outside of the estrual proliferation.

(*b*) In animals with a long corpus luteum stage and in those having pseudopregnancies there is considerable development of the breasts at that time, followed even by secretion of milk.

(*c*) In those animals in which the corpus luteum stage is normally short and in which this has been prolonged artificially, the growth of the mammae can be brought up to equal the condition in pregnancy.

(*d*) "None of the changes characteristic of the luteal phase are found after ovariectomy or removal of corpora lutea."[7f]

With these facts in mind, the clinical and pathologic aspects of the matter may be considered. It was held until recently that inadequate development of the graafian follicle caused chronic hyperplasia of the endometrium because, although the stimulus for growth might not be so powerful as when a normal corpus luteum was formed, the stimulus for regression did not occur, and the proper shedding of the endometrium was interfered with. Each time that a follicle attempted to ripen the endometrium would grow, but since the follicle failed to mature, the cycle was not completed. If only a small portion of the endometrium was thus affected, the result would be the so-called mucous polyp. Applying this theory to the breast, Moszkowicz[8] con-

7. (*a*) Engle, E. T.: Proc. Soc. Exper. Biol. & Med. **25**:715, 1928. (*b*) Evans, H. M., and Simpson, M. E.: ibid. **26**:595, 597 and 598, 1928-1929. (*c*) Nelson, W. O., and Pfiffner, J. J.: ibid. **28**:1, 1930. (*d*) Zondek, B.: Klin. Wchnschr. **9**:241, 1930; abstr., J. A. M. A. **94**:1272, 1930. (*e*) Parkes, A. S.: Internal Secretions of the Ovary, New York, Longmans, Green & Co., 1929. (*f*) Brit. M. J. **2**:1635, 1931.

8. Moszkowicz, L.: Arch. f. klin. Chir. **144**:138, 1927.

tended that so-called chronic mastitis was a generalized irregular hyperplasia, and fibro-adenoma, a localized hyperplasia of mammary tissues, and that both had their origin in ovarian dysfunction. However, this theory cannot be accepted in its entirety, for, as is now known, menstruation occurs in the absence of ovulation and formation of corpus luteum and can take place from interval endometrium. It is therefore not set in action by the withdrawal of the corpus luteum hormone. Allen [9] showed that menstruation could be brought on in ovariectomized monkeys after a series of injections of estrin. Recently Hartman [10] proved that estrin had no effect in the absence of the pituitary gland. If this is true at least two hormones are at work in bringing about sexual cyclic changes. One from the corpus luteum (itself a product of stimulation by the pituitary gland) is concerned in hyperplasia of endometrium and breast; one from the pituitary gland (activated by estrin from the ovary) causes involution.

Moszkowicz's theory has therefore to be widened to include pituitary dysfunction also. He himself did not offer proof of his hypothesis, and much experimental work has yet to be done before it can be definitely established. Still the theory forms a starting point for further investigation.

The easiest method of approach is to inquire into the origin of the growth called by various names, such as "fibro-adenoma," "adenofibroma," "periductal fibroma" and its varieties. If it is true that all these growths are the result of a local aberration of the menstrual cycle, the names lose their importance. They are only descriptive adjectives and serve merely to indicate different appearances in what is essentially a single pathologic entity. In the same way, a surgeon may speak of a carcinoma as "scirrhous," by which he means that there is a particular reaction of the patient's tissues, not any essential difference in the carcinoma as such. This example is not quite on all fours with fibro-adenoma, because in the latter the fibrous tissue is a part of the lesion; in carcinoma, it arises as a reaction of the host, but the analogy will serve. If fibro-adenoma is the result of a local irregularity of the cyclic changes in the breast, it must be produced by proliferation (which may be normal or may be excessive or irregular) followed by incomplete regression or by no regression. If this excess of growth over regression takes place at each cycle, it is easy to see that the result will be a tumor. As the tumor grows, it pushes aside the mammary tissue, thus forming a capsule for itself. The ultimate appearance of the growth of course depends on which of the tissues have

9. Quoted by Parkes.[6]

10. Hartman, C. G.; Firor, W. M., and Geiling, E. M. K.: Am. J. Physiol. **95**:662, 1930.

been most concerned in the proliferation. Just as in a mucous polyp the proportion of glands to stroma is not constant, so in fibro-adenoma the proportion of epithelium to fibrous tissue varies. Moreover, the variation is much greater than in a uterine polyp, because in the breast fibrous proliferation and regression are a necessary part of the sexual cycle. This great variation in fibrous as well as in epithelial growth is the reason why so many names have been given to what is after all one pathologic entity. Suppose, for instance, that epithelial hyperplasia takes place during the premenstrual phase, but that no regression occurs. With each period, the affected lobules undergo further proliferation. The result is the so-called adenoma. If the cells come to the stage of secretion and no absorption occurs, the obvious result will be cysts of the acinar type. It is hardly necessary to postulate a blocked duct, for if there is no mechanism for collapsing the lobule, the cysts tend to remain in situ. When one remembers the comparative rarity of discharge from the nipple as a menstrual phenomenon, it appears that passage of menstrual secretion and shed cells into larger ducts does not take place on any great scale. Suppose, on the other hand, that the chief fault is an overgrowth of the fibrous tissue. The ducts try to proliferate in the premenstrual phase but they are pressed on and pulled out by the fibrous tissue, and the result is the ordinary intracanalicular type of fibro-adenoma.

Theoretically, therefore, the following elements are open to variation in fibro-adenoma (and this applies equally to the generalized lesions of "chronic mastitis" or mazoplasia): the amount of epithelial proliferation and regression and of lobule formation, the quantity of secretion poured into the ducts, and the growth and regression of the pericanalicular fibrous tissue. The possible combinations and permutations are too numerous to mention, but they more than account for the variations observed. The point now is to offer proofs of the correctness of this hypothesis.

If a fibro-adenoma is merely the result of local disturbance in the regular growth and involution of mammary tissue, it should be possible to trace in it some sort of sexual cycle, albeit an abnormal one. With this object, a number of cases have been investigated. For most of these I am indebted to my surgical colleagues, who were good enough to allow me to examine their patients and obtain the histories, and also to collect the tissues for examination immediately after operation. For the purpose of this study a full and reliable menstrual history with the date of onset of the last period was essential. This information is unfortunately missing in most hospital records, and, as so often happens in collecting cases, when a satisfactory history was recorded, the pathologic sections were incomplete or missing. For this reason, the

number of cases that could be usefully studied is small. However, through the kindness of the authorities of the Woman's Hospital and of the Lankenau Hospital, in both of which the records are exceptionally complete, it has been possible to bring the number of fibro-adenomas studied up to twenty-two. Whenever possible, a section from mammary tissue was taken as well as from the tumor. The material was fixed in Bouin's solution of picric acid and formaldehyde. Formaldehyde fixation, which is commonly used in routine work, is not satisfactory from the point of view of cytology, although this material shows general changes well enough.

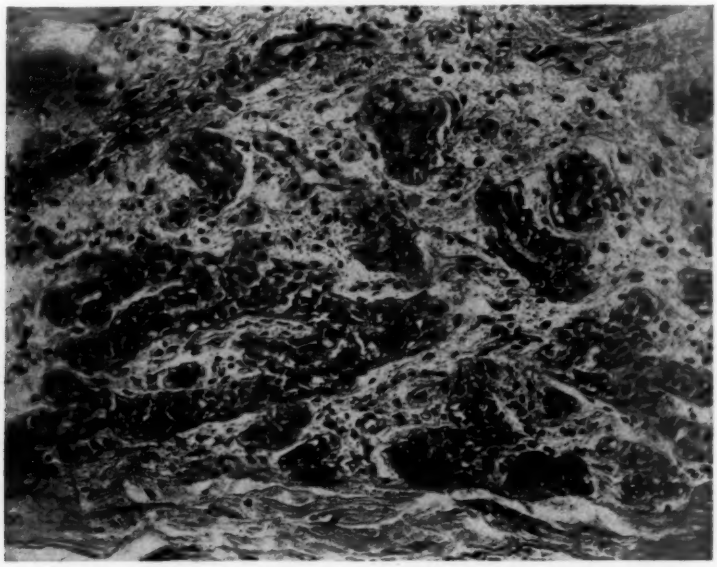

Fig. 1 (M. C., aged 35).—Breast six days before the onset of menstruation; part of a lobule showing branching of the ducts, premenstrual type of epithelium and periductal connective tissue; × 200.

CYCLIC CHANGES IN FIBRO-ADENOMA

Premenstrual (Figs. 1 and 2).—M. C., aged 35, married, had had a mass in the left breast eight years, which had steadily increased in size. She menstruated regularly every twenty-eight days. The operation took place six days before a menstrual period was expected. The tumor, measuring 4 by 3 cm., was smooth and encapsulated. Microscopically, it consisted of ducts resembling those of the breast and more or less arranged in lobules. The lobules lay much closer together than in the normal breast, but they resembled those of the premenstrual phase. Some of the ductules were slightly dilated. Some were branched. The epithelium was premenstrual, i. e., the cells were large and pale, and the epithelial outline was irregular. This feature was most marked at the periphery of the tumor. The tissue between the ductules consisted of loose, edematous fibrous tissue. The breast

showed marked premenstrual proliferation, the lobules being exceptionally developed as regards both epithelial proliferation and loosening of the periductal tissue.

In this case, three characters of the premenstrual phase were present in the tumor—lobule formation, epithelial changes and loosening of the periductal fibrous tissue—although, as would be expected, none were as well developed as in the surrounding breast. Seven other patients ranging in age from 18 to 37 had fibro-adenomas removed during the premenstrual phase. In every case, the tumor showed definite premenstrual characters.

Menstrual (Figs. 3 and 4).—W. M. C., aged 23, single, noticed a growth following a blow received on the right breast when she was 13. The breast had

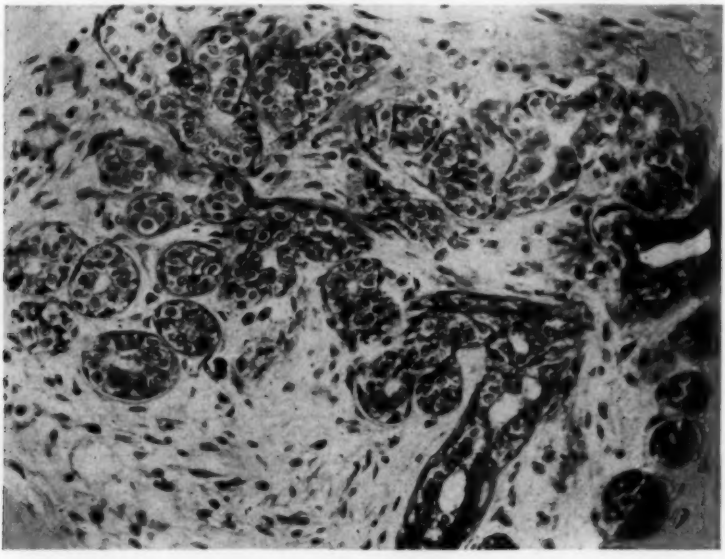

Fig. 2.—Fibro-adenoma six days before the onset of menstruation, from the same breast as the section pictured in figure 1. It shows lobule formation, branching of the ducts, premenstrual type of epithelium (although proliferation is not as marked as in the breast) and loose connective tissue; × 200.

been tender at menstrual periods ever since, also when she had a cold and during attacks of tonsillitis. The growth remained unchanged, except that it enlarged slightly at the time of the menses.

The patient menstruated first at the age of 13; the menses were irregular at first, but at the time of examination were regular. The tumor was removed on the second day of a menstrual period. Grossly, it was a tough, white, lobulated mass, 3.5 by 1.5 cm. With it was a small piece of breast.

Microscopically, the breast was typical of the menstrual phase. Well formed lobules were present. The epithelium was swollen and irregular, and the cells of the basal layer were much vacuolated as though they were about to disintegrate with shedding of the whole epithelium as the result. The periductal connective

tissue was still edematous, but showed commencing proliferation, as is usual after menstruation. The tumor consisted of ducts and lobules resembling those of the breast, except that they were more closely packed together. The lobules were especially well marked toward the periphery of the tumor. The interlobular tissue was dense; the periductal tissue resembled that of the breast. The similarity of mammary and tumor epithelium was striking; in the tumor, the menstrual character was only slightly less developed than in the breast.

Fig. 3 (W. M. C., aged 23).—Breast on the second day of a menstrual period; high power magnification to show the normal vacuolation of the cells of the basement layer.

Two other tumors were removed during menstruation at a slightly later stage. They showed desquamation of epithelium in both tumor and breast.

Postmenstrual (Fig. 5).—S. N., 27, had had a tumor in the left breast for six months. She had been married for eleven months, with no pregnancy. The tumor was removed nine days after the commencement of a menstrual period. It was a lobulated, encapsulated mass, 3.5 by 2.5 cm. No mammary tissue was taken.

Microscopically, there were numbers of ducts embedded in fibrous tissue. Many of the ducts were considerably dilated. Some contained secretion. The epithelium was desquamated into the ducts in many places. Where it was present, the cells were small and regular (typical resting epithelium). In many places, a jumble of desquamated epithelial cells was found in the midst of connective tissue. The appearance was exactly like that seen in the postmenstrual phase in a normal breast, and undoubtedly represented lobules in process of involution. The connective tissue was homogeneous and fairly dense as in the late postmenstrual or in the interval phase.

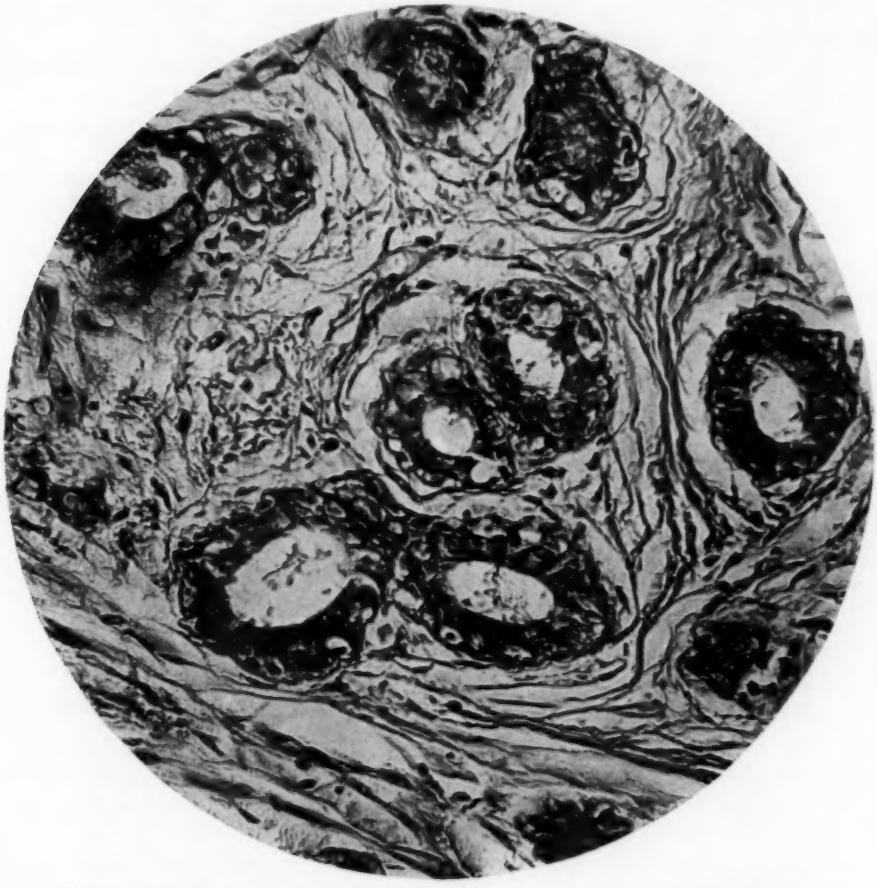

Fig. 4.—Fibro-adenoma on second day of menstruation, from the same breast as the specimen shown in figure 3. Vacuolation of the cells of the basement layer is marked, although not so advanced as in the breast. In both the periductal tissue is loose.

In this tumor, some lobules underwent involution, but not all. Those that did not regress remained as groups of dilated ducts, the lobule formation being gradually lost, owing, no doubt, partly to pressure of the surrounding fibrous tissue and partly to pressure of the cystic ducts themselves.

In another case of a tumor removed seven days after the onset of a menstrual period, postmenstrual regression had only just begun, but breast and tumor showed the same character.

Interval (Figs. 6 and 7).—S. F., 22, single, noticed a tumor eight months previous to operation. The breasts were painful before menstrual periods, but the tumor did not alter. The menses were regular; the rhythm, $\frac{28}{5}$. The onset had been at the age of 12. The tumor was removed fourteen days after the commencement of a menstrual period.

Microscopically, the tumor consisted of fibrous tissue in which were embedded elongated ducts. Nowhere in the tumor was there any indication of lobule formation. The epithelium lining the ducts was regular, the nuclei stained deeply, and

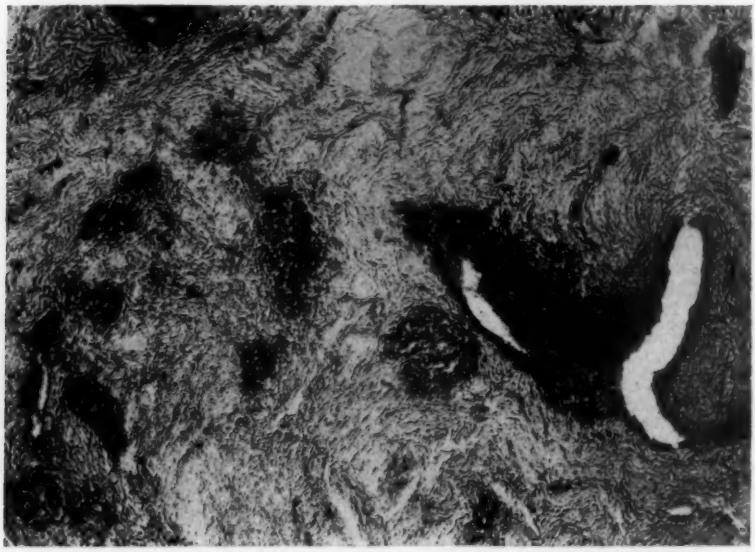

Fig. 5 (S. N., aged 27).—Fibro-adenoma removed nine days after the onset of menstruation. It shows well marked postmenstrual involution in some parts of the tumor and dilated ducts in others. Fairly dense connective tissue is shown; × 50.

there was no vacuolation of the protoplasm. In the mammary tissue, the lobules varied a little. Most were typical of the interval phase; a few showed early premenstrual budding. Overgrowth of fibrous tissue was the most conspicuous feature of this tumor, possibly preventing complete regression of the ducts.

Three other cases in which the tumors were removed in the interval phase showed typical interval epithelium with no proliferation of ductules.

Amenorrheic.—One tumor, in a girl of 16, was removed during a period of amenorrhea. Microscopically, there was nothing characteristic of any special phase of the sexual cycle. There was irregular proliferation of the epithelium, but the cells were small. The connective tissue was loose, but lobules were not present.

Postmenopause (Fig. 8).—In E. A., aged 52, the menopause occurred ten years previous to operation. The lump in the breast had been noticed some weeks before operation.

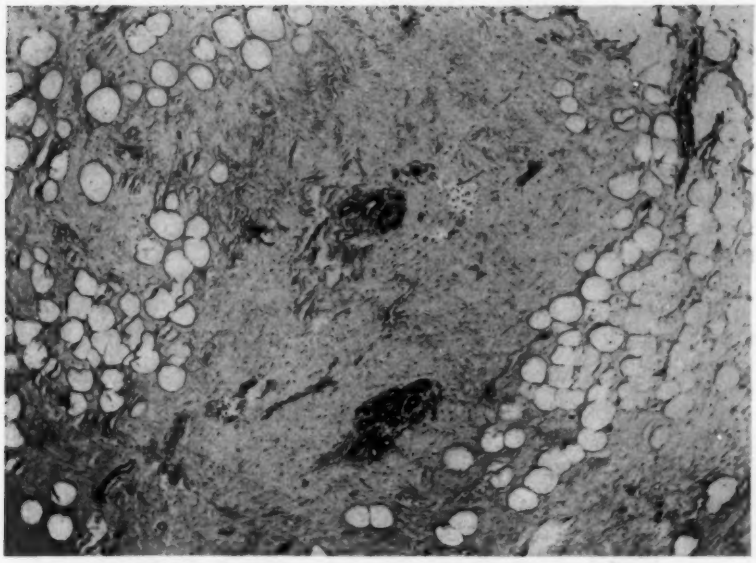

Fig. 6 (S. F., aged 22).—Breast fourteen days after the onset of menstruation —the interval stage—showing small groups of ducts with deeply staining, regular epithelium. Traces of former lobules that have undergone involution can be made out in the connective tissue.

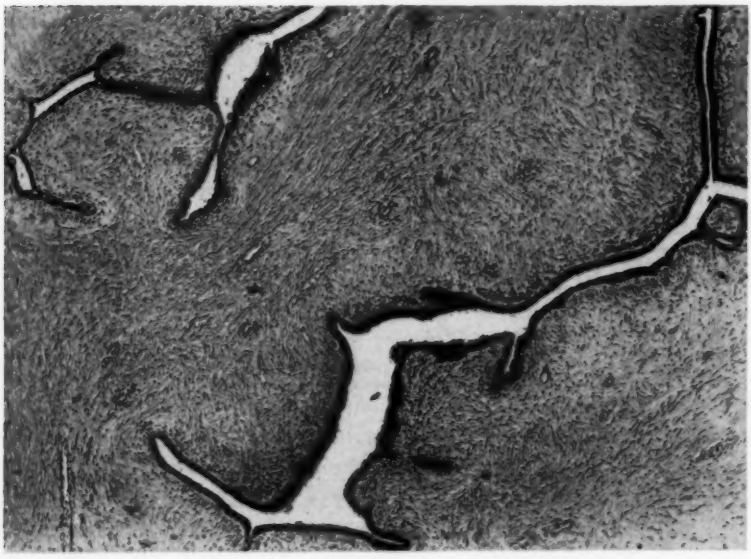

Fig. 7.—Fibro-adenoma fourteen days after menstruation from the same breast as the section shown in figure 6. There is no lobule formation. The epithelial cells are small. The fibrous tissue is deeply staining and uniformly dense; it appears to be rather more dense around the ducts.

Microscopically, the breast showed the ordinary senile changes. It consisted of fibrous tissue and fat, in which ductules with inactive epithelium could be seen here and there. The tumor consisted mainly of dense fibrous tissue. In some places, however, there were ducts that had been distorted by the growth of the fibrous tissue (so-called intracanalicular type of tumor). The epithelial cells were small and showed no sign of proliferation; some had been shed, leaving only a basement membrane. This tumor seems to have been caused purely by overgrowth of fibrous tissue. It showed nothing indicating any kind of sexual cyclic change.

The nineteen cases just described were uncomplicated in the sense that as far as was known there was no disturbance of mammary tissue

Fig. 8 (E. A., aged 52).—Fibro-adenoma ten years after the menopause, showing dense fibrous tissue, distorted ducts and degenerate epithelium.

other than the fibro-adenoma. In seventeen cases there was a regular or almost regular menstrual cycle. In the two in which tumors were removed during a period of amenorrhea and after the menopause, the growths showed no definite changes belonging to the sexual cycle. In the other tumors, the stage of the cycle could always be recognized, sometimes easily, sometimes only after careful study. The recognition of the cycle in tumors seemed difficult at first, but with practice it has been found possible to date tumors fairly accurately without other information than the microscopic section of the growth. It is not to be expected that all the changes that occur in the normal breast during

the sexual cycle will be found in tumors. If this happened, there would be no tumor. New lobule formation, for example, was found to some extent in all of the tumors removed during the premenstrual stage. It was generally seen near the edge of the growth, probably because the tissue was able to expand in this direction. The central parts did not show it nearly so often. Regression of lobules was seldom complete, and sometimes did not appear to have taken place. In the interval tumors, no definite lobular formation was present. The elongated, branched ducts so often seen are doubtless the distorted remains of lobules. One is enabled to judge between newly formed and old lobules because the latter are almost sure to be distorted by pressure of the surrounding tissues and by distention from their own secretion. The periductal tissue may agree with the stage of the sexual cycle, but is likely to be abnormal. In ten of fourteen cases it was definitely abnormal. Once it was excessively hyaline. Three times hyaline degeneration accompanied an excessively dense tissue. Once it was edematous and loose during the interval phase. In the remaining five cases, the fibrous tissue was dense and overgrown, i. e., excessive even for the interval phase. Probably the most constant criterion of the menstrual date is the appearance of the epithelial cells. In all these cases it was characteristic at least over the greater part of the tumor. As with lobule formation, the change tended to be best defined in the peripheral parts of the growth. In general, it may be said that while the indications of cyclic changes are clear, they are never exactly the same as in the normal breast. Usually the development is not perfect and lags behind that of the breast. Often it is excessive in certain directions (epithelial or fibrous tissue proliferation). The periphery of the growth is usually more nearly like the normal breast than the center. Often normal mammary lobules are caught up in the capsule, indicating that they may in turn come under the influence of aberrant stimuli and eventually form part of the tumor. However, the fact that new lobule formation takes place at the periphery of the growth suggests that it is proliferation in response to cyclic stimuli that is chiefly responsible for its increase in bulk.

Clinical confirmation of this view is found in the number of cases in which the tumor was first noticed just before a menstrual period, and in which an increase in size (sometimes followed by a decrease after the period) was noted at this time. Of seven patients of whom the question was specifically asked, two gave a history of the lumps being noticed just before a menstrual period and three others of increase in size just before or at the time of periods.

If proliferation occurs in a fibro-adenoma during the premenstrual phase, one might expect a much greater increase during pregnancy and

lactation. McFarland [11] reported such cases and described lactation in one tumor. A description of a case of lactation hyperplasia in a fibroadenoma follows:

M. F., aged 18, married, complained of a large tumor in the left breast. At 6 years of age she had fallen on the left breast. It was painful for some time, but she never noticed lumps until she began to menstruate at the age of 13. At this time, the left breast became somewhat painful and nodular, but did not increase in size. This continued for some time, but subsequently subsided and gave no trouble. The menstrual periods were regular. She was delivered of her first child ten months before coming to the hospital. Following this, she had a painful swelling in the left breast and was told she had a "caked breast." The swelling gradually increased and was painful at times. She did not nurse her child except for the first few days. On examination, a mass the size of a small grapefruit was found in the outer half of the breast. The tumor was firm and somewhat tender. The veins over the breast were markedly dilated. At operation the tumor was found to occupy the greater part of the breast. The breast was therefore removed along with the growth.

The tumor was a smooth encapsulated mass about 10 cm. in diameter. The cut surface was honeycombed with small cysts. These gave a somewhat spongy feel to the whole mass.

Microscopically, the tumor showed numerous very large, branched, distended ducts (fig. 9). The epithelial cells lining them had an unusual appearance, for in most places a sort of tuft projected from their protoplasm. This was evidently a cell secretion, for the tufts varied in shape, and sometimes the material formed a rounded mass that hung by a thread from its parent cell. The nuclei of the cells were fairly large and clear staining. The cells of the basal layer were swollen and vacuolated. Near the large dilated ducts, groups of smaller ones showing the characters of a lactating breast might be found. Sometimes the large ducts were embedded in fat, but more often they were surrounded by peculiar cellular areas, which frequently filled the spaces between them. In these areas, irregular, vacuolated cells lay in clumps or were scattered through the tissue. They had the same characters as the epithelial cells, but their nuclei were extremely irregular and vacuolated, and their protoplasm was reduced to shreds, giving them a stellate appearance resembling that seen in myxomatous tissue. Sometimes remains of ducts could be made out.

These areas with their absence of any regular architecture were comparable to the postmenstrual phase of the sexual cycle and recalled strongly the appearance seen in involution following lactation. The disorganization could not have been due merely to pressure from the dilated ducts, because in some places, as has been said, groups of regular ductules were present. In this tumor, lactation involution seems to have progressed up to a certain point, but not to have been satisfactorily completed. It would seem that the stimulus toward lactation had not ceased to act.

The breast was reduced to a shell around the tumor and was therefore much compressed. In spite of the compression it showed well marked involution of the type that follows lactation. There were large lobules, the outer part of which consisted of young fibrous tissue and the center of branching ducts, many of which were dilated and filled with epithelial cells in various stages of degeneration. Sometimes ductules were replaced by a jumble of cells; the cells resembled those of the tumor but were smaller.

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11. Deaver, J., and McFarland, J.: The Breast, Philadelphia, P. Blakiston's Son & Co., 1916, p. 447, and illustrations, p. 448.

Dr. Otto Saphir of Chicago sent me particulars of a case on which he and Dr. Irving F. Stein are about to publish a report—a case of pregnancy hyperplasia in a fibro-adenoma. In a woman, aged 21, who had been pregnant for two months, a tumor of the left breast developed, which was removed immediately. The photomicrograph (fig. 10) shows proliferation of ducts and acini which, although irregular in places, bear considerable resemblance to those found in normal lobules

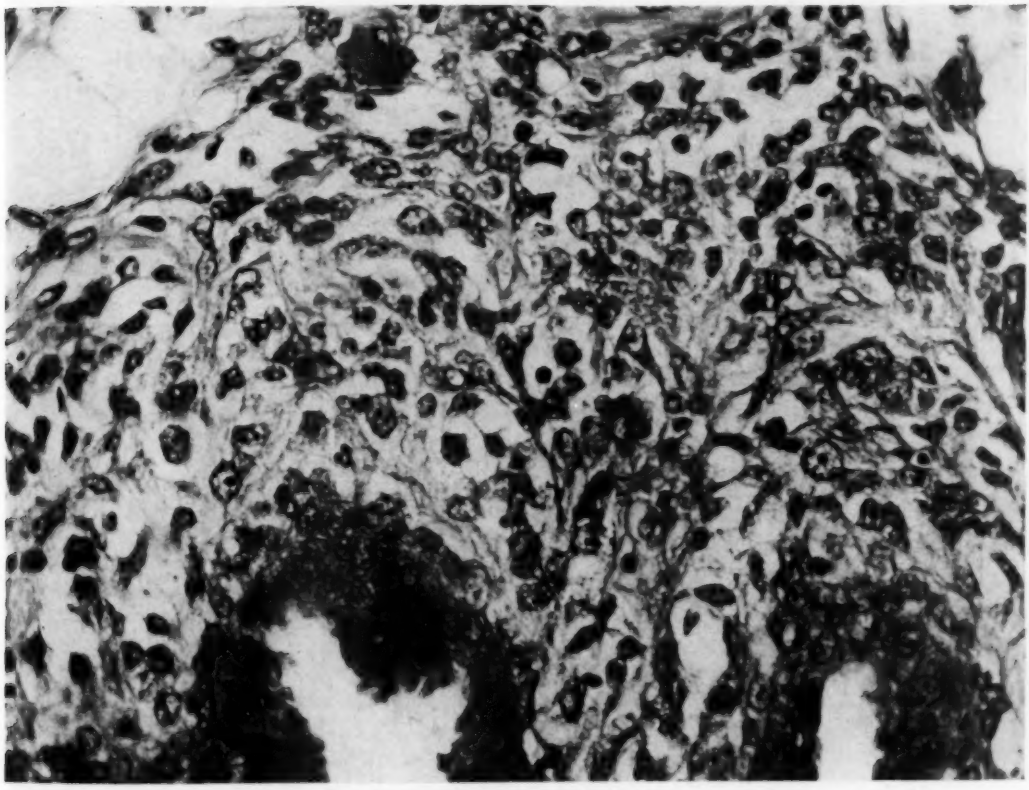

Fig. 9 (M. F., aged 18).—Fibro-adenoma of breast ten months after parturition; high power magnification to show lactation involution.

during pregnancy. The interesting point is that five pictures from different parts of the growth show absolutely no indication of involution, which was such a prominent feature in the lactation tumor described in the preceding paragraphs.

From a study of the cases described in this paper, one may fairly conclude that *the changes in a fibro-adenoma parallel those of the breast.* Nevertheless, it may be objected that this does not prove that the tumor first arose owing to a local aberration in the sexual cycle. There may

have been some other cause, and the sexual changes might be secondary. In reply one may say that of course there must have been an exciting cause, as perhaps trauma, which provoked the irregularity in one part of the breast rather than in another, but it seems extremely probable that the mechanism of formation of the tumor is as suggested. McFarland [12] in 1918 put forward the theory that "the tumor is primarily a lobule of breast tissue aroused to growth through unknown stimuli."

An argument in favor of fibro-adenoma being nothing more than the result of local dysfunction in a lobule is the difficulty often found

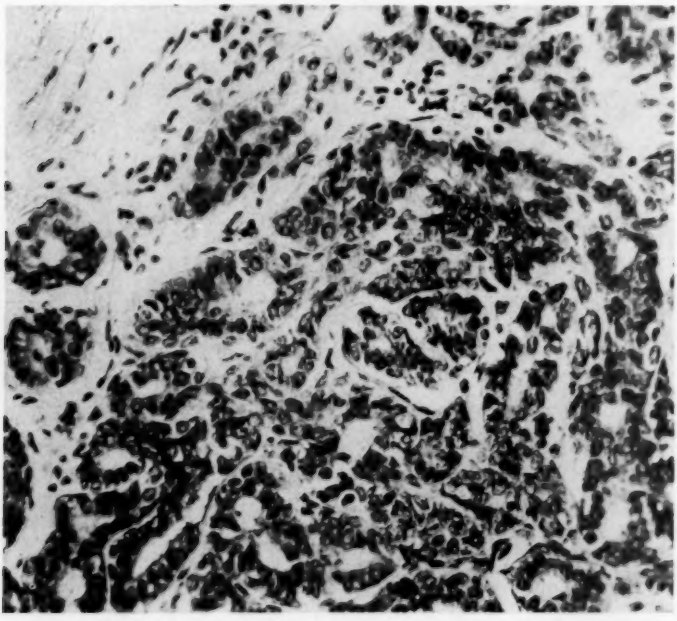

Fig. 10.—Dr. Saphir's case of a fibro-adenoma removed during pregnancy. It shows pregnancy hyperplasia.

in deciding from microscopic sections whether one is dealing with a tumor or not. In one case, after it had been decided that the section was that of a resting breast in which postmenstrual involution had not been complete, a gross description was found in which it was stated that the tumor was completely encapsulated and had been shelled out without the removal of any mammary tissue. McFarland [5] in his analysis of some three hundred cases was faced by the same difficulty; in one hundred and forty-seven cases called instances of "tumor" by surgeons and pathologists, he found only normal mammary tissue; in thirty-seven

12. McFarland, F.: Arch. Surg. **5**:1, 1922.

cases, he found it impossible to decide whether a tumor was present or not. The same problem arose in this small series. Unless a gross description is available, it may be impossible to distinguish between a fibro-adenoma and one or other form of so-called chronic mastitis, which it is preferable to call mazoplasia after Cheatle,[13] or even between fibro-adenoma and normal breast. The only distinction that would enable one to decide in these cases would be the presence or the absence of a capsule. Of course, some tumors have characters that do not show themselves in a generalized mazoplasia, such as the extreme pulling out of ducts by fibrous tissue, but a lesser degree of the same thing is often seen, and it would seem likely that special characters are the result as much of compression by the surrounding breast as of a particular kind of growth. Many of these tumors are semi-encapsulated showing complete continuity with normal breast on one side and sharp demarcation from mammary tissue on the other. It is easy to see how such a situation would arise from proliferation of a lobule or of a group of lobules.

Therefore since the transition from fibro-adenoma to mazoplasia is such a gradual one, and since the line between the normal and the abnormal in the breast is so hard to draw, it seems reasonable to postulate a gradual transition from the physiologic to the pathologic. In other words, aberrant physiologic stimuli are more likely to be the etiologic factor than an extraneous cause unconnected with the sexual cycle. The probability is enhanced if it is possible to show a close connection between hormonal disturbance and the pathologic condition in the breast.

MAMMARY CHANGES IN PATIENTS WITH IRREGULAR SEXUAL CYCLES

Young Women.—E. R., aged 17, single, had a small nodule in the right breast. Menstruation began when she was 17 years old. The periods were irregular, menstruation occurring about every two months. She menstruated forty-six days before operation, and she did not menstruate again until forty-six days after operation. She had three attacks of appendicitis before coming into the hospital. A chronically inflamed appendix was removed as well as a tumor of the breast. The tumor is said to have been "the size of a strawberry."

Microscopically, the mammary tissue showed every kind of irregularity. There were cystic ducts, some containing proliferated epithelium. Lobules were present, somewhat resembling those of the menstrual or postmenstrual phase, and in many places the dilated ducts showed a lobular grouping. The extreme, irregular epithelial proliferation would have earned the title of precancerous mastitis had the section been examined some years ago. The tumor showed groups of dilated ducts arranged more or less in lobular fashion in loose, edematous connective tissue. Two similar cases in girls aged 16 and 18, respectively, were studied.

13. Cheatle, G. L.: Arch. Surg. **17**:535, 1928.

Cheatle [13] in 1928 called attention to the resemblance between this condition and "chronic mastitis" and to the etiologic association between general active changes at puberty and the formation of fibro-adenoma.

Woman of 33.—L. C., aged 35, married, complained of a lump in the left breast, which had been present for six months, gradually increasing in size. She had been married eleven years and had had four children, also one miscarriage at two months one year before admission. The onset of menstruation was at the age of 13; the rhythm was $\frac{30}{3\text{-}4}$; the menstrual periods were irregular, sometimes being as much as six weeks late. There was moderate dysmenorrhea. For the past two years, the flow had been very scanty and had lasted only one day; menstruation had been followed by epistaxis. Flushings and headaches took the place of periods. Such a condition occurred one week after operation for removal of the breast.

Microscopically, the breast showed premenstrual characters, but with considerable hyperplasia of lobules and ducts. There were numerous cysts filled with shed epithelium, also moderate hyperplasia of the lining membrane of the large cystic ducts. Around some of the ducts were groups of lymphocytes; probably they appeared in response to irritation by the degenerated contents of the cysts. No circumscribed tumor was found.

This patient reported again two and one-half years later. The periods were still scanty and slightly irregular, but much less so than when she was in the hospital. She complained of pain in the remaining right breast at times, the pain being worse before a period. On examination twenty days after the last period, one dilated duct could be felt in the breast.

In this case, it would seem that the condition of the breast improved with the improvement in regularity of the cycle, but the menstrual function was still abnormal, and the condition of the breast had not completely cleared up.

Cases of irregular proliferation of the breast in women around the age of 40 are so common that individual instances need not be recorded here. Many are associated with pelvic lesions. As is well known, menstrual irregularities tend to occur at puberty and at the menopause. In women nearing the menopause, even if menstruation is regular, various alterations in the body indicate an alteration in the balance of the hormones. Every surgeon is aware of how common lesions of the breast are at this time. It must be emphasized that, although irregularity of the menses is accompanied by irregularity of development and involution during the sexual cycle in the breast, it does not follow that the factor responsible for menstruation is the same as that governing the changes in the breast.

Stress has been laid on menstrual irregularity in mazoplasia because it is the most obvious and the most trustworthy evidence of hormonal alteration at one's disposal. It is the best index that one has that the cycle is disturbed. The converse, that because menstruation is regular the cycle is not disturbed, is obviously not true, as experimental work shows. Otherwise, the number of cases of mazoplasia in which

menstruation is regular would be amply sufficient to refute the argument put forward here. It would be exceedingly interesting to discover whether the endometrium is really normal in the latter cases, but there is not often the opportunity of examining specimens from the breast and endometrium of the same patient.

The next question is: Do cases of generalized mazoplasia occur in which ovarian dysfunction can be excluded? This is an extremely difficult question to answer. There is no doubt that certain causes will provoke an attack, but whether they will do so in the absence of any hormonal imbalance can probably be settled only by animal experiment. Since such attacks occur practically always in middle-aged women, it looks as though there must be an underlying hormonal factor. An important exciting cause is trauma. A history of trauma occurs frequently both in fibro-adenoma and in mazoplasia. In many cases, however, it is denied. Hammett,[14] demonstrated the part played by injury in releasing the growth-promoting SH radical. Injury undoubtedly increases any preexisting hyperplasia, and there seems no reason why it might not upset the normal growth and regression of the sexual cycle, although it is perhaps harder to see why it should continue its effects indefinitely. However, the continued effect might be attributed to mechanical disturbances from the proliferated fibrous tissue. Mechanical disturbances appear to be of considerable importance. Another exciting cause is the ingestion of certain substances, notably strawberries. Possibly certain persons might react by swelling of the breasts to any substance to which they were hypersensitive, but, as far as I know, no observations have been published on this point. Exposure to cold may be an exciting cause—it undoubtedly tends to increase mazoplasia when it is present, as also does the ingestion of alcohol, especially wines.

Inflammation, which has been regarded as such a potent factor in the past, has not been found an etiologic factor in the cases concerned here. Groups of round cells, it is true, are often present in the neighborhood of dilated ducts, but they can more easily be interpreted as an effect of irritation from the distended ducts and cell débris within them than as the cause of the lesion. The fact is that when inflammation occurs, it does not produce mazoplasia.

MASTITIS WITHOUT ABNORMAL CYCLIC CHANGES

E. W., aged 28, single, had suffered from soreness and enlarging and hardening of the right breast for six months. It was tender and seemed more prominent at

14. Hammett, F. S.: Protoplasma **4**:103, 1928; **7**:297, 1929; Proc. Am. Philos. Soc. **68**:151, 1929. Hammett, F. S., and Reimann, S. R.: J. Exper. Med. **50**:445, 1929.

the menstrual periods. She had had otitis media. There was a discharge from the right ear while she was in the hospital. Menstruation was regular, with onset at 11 years and rhythm $\frac{28}{6}$. A diagnosis of chronic cystic mastitis was made, and the breast was removed fourteen days after a menstrual period.

Microscopically, the breast was in the interval phase. There was nothing suggestive of any disturbance of the sexual cycle. The chief abnormality was a great excess of young, branched fibrous tissue cells that compressed many of the ducts. Other ducts were surrounded by masses of lymphocytes, in far larger numbers than is seen in mazoplasia. This case could be truly labeled "chronic mastitis;" the lesion was obviously inflammatory.

Three other cases were studied. A girl of 19 had three abscesses in her breast in the course of a year. A sinus was excised on the first day of a menstrual period. In spite of severe inflammation, the adjacent tissue of the breast showed normal menstrual features.

A Negro woman of 40 had had a tuberculous infection of the breast for sixteen years. The organ was riddled with sinuses. It was excised just before a menstrual period was due. Where mammary tissue still remained, there was no disturbance in the development of the lobules, which were typically premenstrual.

In a woman of 39 who had irregular menstrual periods and also a chronic abscess, the mammary tissue at a distance from the abscess showed very irregular proliferation, while that within the zone of inflammation was more nearly normal.

The conclusion to be drawn from these cases would seem to be that inflammation alone does not affect the mammary cycle and is not a cause of mazoplasia. In view of the clinical connection between menstrual irregularity and mazoplasia it seemed worth while to see whether it was possible to produce changes similar to those of chronic mastitis in the breasts of animals by altering the estrual cycle.

In the rat, intercourse with a vasectomized male induces pseudopregnancy and changes the menstrual cycle from the normal four or five days to approximately ten days. As a preliminary experiment, ten female rats were placed with two vasectomized males. This was evidently too high a proportion of females, for in two of them the cycle did not change, and in the others there were periods of a return to the four day cycle. Four young rats showed regular increase in size of the lobules of the breast, the expected physiologic response to a prolonged cycle. Two older rats had a rather irregular epithelial hyperplasia, and two showed a well marked cystic condition of the breast with very irregular development of the lobules that were not cystic. In all the animals, pieces of mammary tissue removed before the experiment were normal. In order to be sure that the hyperplasia had nothing to do with trauma from previous operations, the experiment was repeated with nine new rats. In four, hyperplasia and cysts developed. It would be premature to draw conclusions from such small numbers. Investigations along these lines are being continued, and it is hoped to publish a full report later.

SUMMARY

In twenty-one cases of fibro-adenoma of the breast, a comparison of tumor and breast from the same patient showed that in patients with a regular menstrual cycle the same type of cyclic change was found in the tumor as in the adjacent normal breast. It was found possible to diagnose the stage of the cycle from an examination of the tumor alone.

One tumor was removed during pregnancy and one after parturition. The former showed hyperplasia resembling that occurring during pregnancy; the latter had characters partly of lactating breast and partly of involution following lactation.

In four cases in which the menstrual periods were irregular, it was not possible to assign the tumor to any special phase of the cycle.

Hyperplasia with growth of new lobules occurs regularly in fibro-adenomas during the premenstrual phase of the sexual cycle. This is most easily seen at the edge of the tumor. Involution is often incomplete. Hyperplasia of periductal fibrous tissue may be in excess of the normal. It follows that a fibro-adenoma is the result of a local irregularity in growth and regression of the sexual cycle in the breast. What provokes the irregularity is not known.

Disturbance of the balance of hormones concerned with the sexual cycle may be considered the most important etiologic factor in mazoplasia. Cases are recorded to show the close association of so-called "chronic mastitis," or mazoplasia, with irregularity of the menstrual cycle, which is taken as an index of hormonal disturbance.

Inflammation is not an etiologic factor in mazoplasia. Three cases of severe chronic inflammation of the breast showed no irregularity in the sexual cyclic changes.

It was found possible to produce a cystic condition and irregular hyperplasia in the breasts of rats by upsetting the estrual cycle.

EXPERIMENTAL PATHOLOGY OF THE LIVER

VII. RESTORATION OF THE LIVER AFTER PARTIAL SURGICAL REMOVAL AND LIGATION OF THE BILE DUCT IN WHITE RATS

GEORGE M. HIGGINS, PH.D.
AND
REUBEN M. ANDERSON, M.D.
Fellow in Surgery, the Mayo Foundation
ROCHESTER, MINN.

Restoration of the liver to normal weight occurs rapidly after partial removal. The liver of the white rat recovered approximately 35 per cent of its preoperative weight the first day following removal,[1] and by the end of the third day it had more than doubled in weight. Factors incident to such a rapid rate of recovery of the preoperative weight of the liver are of great biologic interest, for no other organ, so far as we know, recovers its weight so rapidly following the removal of so large a portion of its parenchyma. Although the cytologic organization of the rapidly restored organ is not quite identical with that of a normal liver, yet there is no indication that any functional disturbance has been imposed. Complete restoration of the liver to its original weight, following removal of about 70 per cent of it, is ordinarily attained in from ten to fourteen days.

In a consideration of the factors that control or regulate this rapid restoration we were interested to know to what extent hepatic injury, such as that imposed by obstruction to biliary outflow, might modify normal recovery. Mann, Fishback, Gay and Green[2] (1931) reported that when biliary obstruction was induced in dogs by double ligation and section of the common bile duct before the liver was partially removed, such remarkable restoration did not occur.

METHOD OF EXPERIMENT

Sixty rats, aged from 6 to 9 months, having a mean body weight of 171.3 ± 4.156 Gm., were operated on. The rats were from the genetic strain used in the earlier studies on hepatic regeneration. With the aseptic method already

From the Division of Experimental Surgery and Pathology.

1. Higgins, G. M., and Anderson, R. M.: Arch. Path. **12**:186, 1931.

2. Mann, F. C.; Fishback, F. C.; Gay, J. G., and Green, G. F.: Arch. Path. **12**:7899, 1931.

described, about 70 per cent of the liver was removed; at the same time, the bile duct was securely ligated but not sectioned. The rat does not have a gallbladder, and thus complications induced by the biliary vesicle in the presence of obstruction did not exist. All animals had free access to a 15 per cent dextrose solution immediately after the operation and were placed on the routine laboratory ration of food and water the following day. To secure data on the weights of the restored parenchyma and the ratios of weight of liver to weight of body following partial hepatectomy, five animals were killed by exsanguination at three days, one week, two weeks, three weeks and four weeks after the operation, and to secure early data with regard to changes in hepatic cells two rats were killed at eighteen, twenty-four, forty-eight and seventy-two hours after operation. Portions of livers were fixed in Zenker-formaldehyde solution and stained with hematoxylin and eosin, with eosin-azur II, and for iron.

Mean Weights of Body and of Moist Liver Before Partial Hepatectomy and Ligation of Common Duct and at Intervals During Restoration

Group	Animals	Lapse of Time After Operation Before Animals Were Killed	Mean Weights: Before Operation, Body, Gm.	Before Operation, Liver Gm.	At Time of Partial Hepatectomy, Liver Removed, Gm.	At Time of Partial Hepatectomy, Liver Remaining, Gm.	At Time of Death, Body, Gm.	At Time of Death, Liver, Gm.	During Restoration, Hepatic Increment (Moist) Gm.	During Restoration, Percentage of Weight of Liver
All animals operated on	60	.....	171.3 ± 4.156	6.21 ± 0.0769	4.36 ± 0.0720					
1.....	5	72 hours	146.8 ± 7.314	5.62 ± 0.2876	3.62 ± 0.0693	2.00 ± 0.2958	136.2 ± 6.289	4.72 ± 0.2960	2.72 ± 0.4184	0.0346
2.....	5	7 days	182.0 ± 11.82	6.48 ± 0.2876	4.46 ± 0.1753	2.02 ± 0.3368	148.2 ± 8.722	6.070 ± 0.3500	4.05 ± 0.4857	0.0409
3.....	5	14 days	188.4 ± 8.94	6.62 ± 0.2876	5.00 ± 0.3642	1.62 ± 0.4646	167.6 ± 7.910	6.950 ± 0.8490	5.33 ± 0.9677	0.0414
4.....	5	21 days	195.2 ± 13.05	6.78 ± 0.2876	4.45 ± 0.0570	2.33 ± 0.2932	184.8 ± 11.36	8.84 ± 0.4150	6.51 ± 0.5081	0.0478
5.....	5	28 days	225.0 ± 11.77	7.51 ± 0.2876	5.70 ± 0.4450	1.81 ± 0.5298	198.0 ± 10.05	6.81 ± 1.0800	5.00 ± 1.2030	0.0344

By means of the formula $y = 0.024\,x + 2.1 \pm \frac{0.5752}{\sqrt{n-1}}$, in which x is body weight and y is liver weight,[1] the preoperative weights of the livers of all experimental animals were estimated. Since the amount of liver removed surgically from each rat was known, the weight of the parenchyma that remained in the peritoneal space after the operation was easily estimated. The average gain in weight of the livers of the five rats killed at each of the designated intervals was computed. The onset and extent of jaundice were observed, and determinations of serum bilirubin were made at the time the animals were killed.

EXTENT AND RATE OF HEPATIC RESTORATION

It was clear from the data assembled during this study, and condensed as shown in table 1, that ligation of the bile duct at the time of partial hepatectomy induced considerable effect on the rate and the extent of the apparent restoration of the organ. The curve of the weights of the restored parenchyma in the presence of biliary obstruc-

tion may be readily contrasted with the curve of hepatic weights at corresponding intervals after partial hepatectomy alone (fig. 1 *a* and *b*).

At the end of the third day after operation, the actual increase in the weight of the liver for each 100 Gm. of preoperative body weight was 1.8 Gm. This is the exact figure computed at the end of the third day after partial removal and splenectomy,[3] and is slightly greater than that computed, after a corresponding interval, when partial hepatectomy alone was done.

At the end of the first week, the increase in weight of the liver was more marked in those animals in which biliary stasis had been induced. An average increase of 2.2 Gm. of parenchyma for each 100 Gm. of

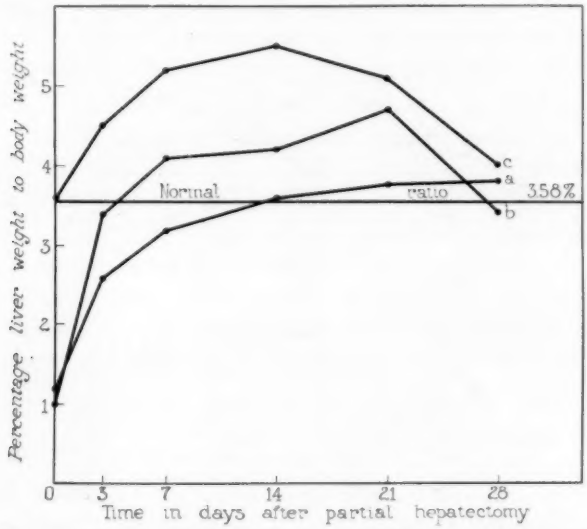

Fig. 1.—Percentage of weight of liver in relation to weight of body during hepatic restoration. The curves represent (*a*) restoration following partial hepatectomy; (*b*) restoration following partial hepatectomy and ligation of common bile duct; (*c*) liver weight per cent of body weight following ligation of common duct without removal of liver.

preoperative body weight was recorded for the rats with biliary obstruction, and 1.6 Gm. had been restored for a corresponding unit of body weight of animals subjected to partial hepatectomy only. The ratio of the weight of the liver to the weight of the body at the time of death was greater by approximately 1 per cent in the series with biliary obstruction.

At the end of the second week, the increase in the weight of the restored parenchyma in the control rats subjected to partial hepatectomy

3. Higgins, G. M., and Priestley, J. T.: Arch. Path. **13**:573, 1932.

only and that in the rats in which there was biliary obstruction were more nearly alike. On the basis of preoperative body weights, an average of 2.8 Gm. of hepatic parenchyma, for each 100 Gm., had developed in animals with obstruction, and only 2.4 Gm. in the control animals. At the end of the third week, however, the increase in weight of the restored parenchyma in animals with biliary obstruction was greater by 0.7 Gm., for each 100 Gm. of preoperative body weight, than in the control rats. Thus it appeared that, so far as the weights of the livers were concerned, biliary stasis had induced increased rates of hepatic restoration.

During the fourth week, the mortality was higher, and the animals that survived to the twenty-eighth day had patent bile ducts; the ligature had been absorbed and continuity with the duodenum was reestablished. Jaundice had disappeared, and determinations of the serum bilirubin were negative. The animals which survived for twenty-eight days, and which were killed at that time for data on the weights of the livers, were normal as far as bile drainage was concerned. It must be assumed, however, in the presence of jaundice and other gross manifestations, that these animals had passed through the period of temporary obstruction. When the data on weights of the livers assembled from these animals four weeks after operation were compared with those of the control rats, the extent of restoration throughout the period was much greater in the group without obstruction. This would seem to indicate that the increased weights recorded when obstruction was present were due not so much to actual restored parenchyma as to retention of bile constituents.

To test the effect of obstruction of the bile duct on the weight of the normal liver, forty rats were operated on. The bile ducts were ligated as before, but the liver was not removed. Total obstruction to the flow of bile induced an immediate increase in the weight of the liver (fig. 1 *c*). Strangely enough, the curve of the ratios of weight of liver to weight of body at the indicated intervals in this series was closely parallel for the first two weeks to that describing the ratios in the rats with biliary obstruction from which the livers had been removed. By the twenty-first day, however, the ratios were lower (fig. 1 *c*), and when biliary continuity was again established, essentially normal ratios were recorded.

Following such obstruction to biliary outflow by ligation, excessive dilatation of the bile duct proximal to the ligature occurred. These dilated ducts often appeared as large pouches, resembling gallbladders, on the inferior surface of the liver (fig. 2), and were often as large as 3 cm. in diameter, even distending the abdominal wall. Occasionally they ruptured, and bile peritonitis then ensued.

JAUNDICE

Jaundice, as determined by its appearance in the sclera, the urine and the viscera, was never grossly visible until the second or third day. In some instances, however, determinations of serum bilirubin revealed, as early as eighteen hours after operation, bilirubinemia of 10.96 mg. for each 100 cc. of blood. Determinations were inconstant in that analysis of the serum varied greatly within any group of animals killed at any given time. The average of the serum bilirubin for all animals killed at intervals was 10.50 mg. at twenty-four hours, 16.05 mg. at forty-eight hours, 13.05 mg. at seventy-two hours, 17.21 mg.

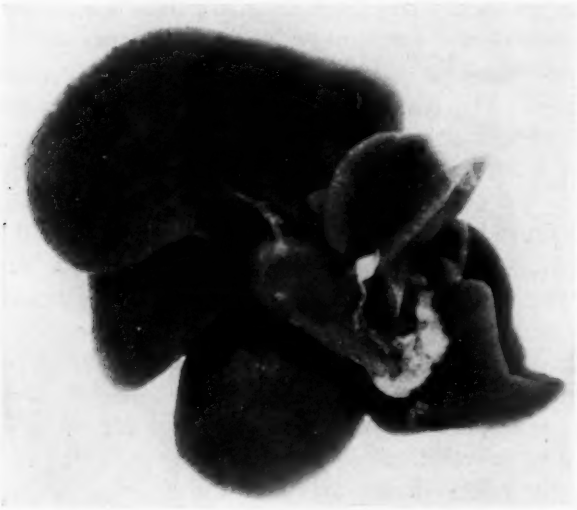

Fig. 2.—Marked distention of bile duct proximal to ligature fourteen days after operation.

at seven days, 12.26 mg. at fourteen days, and 6.44 mg. at twenty-one days. Bilirubinemia was not observed in any animals killed on the twenty-eighth day. The bilirubinemia in animals in which only the duct was ligated did not vary to any extent from that which was determined for those with both hepatic removal and biliary obstruction. In the presence of total obstruction, the amounts of hepatic parenchyma present were without significant effect on the onset or on the extent of bilirubin in the blood.

HEPATIC CYTOLOGIC CHANGES DURING RESTORATION

The cytologic changes that took place in the hepatic remnant during restoration were those of typical biliary cirrhosis with obstruction. Changes, which were induced as early as fifteen or eighteen hours, were progressive and gradually involved most of the lobule. Within a few

hours the canaliculi were distended with inspissated bile, and large globules of bile from ruptured canaliculi often distended the hepatic cells, pushing the nuclei to one side. Another early reaction was an increase in the number and the size of local histiocytes. Erythrocytes were commonly seen within them, and granules of hematoidin, with an unusually large amount of hemosiderin, occurred in the cytoplasm of these Kupffer cells. Obstruction to the flow of bile had induced retention within the cells of the pigments normally elaborated. During the second and third day, the cytoplasm of the hepatic cells was alveolar, filled with innumerable small globules of bile. Prussian blue stains

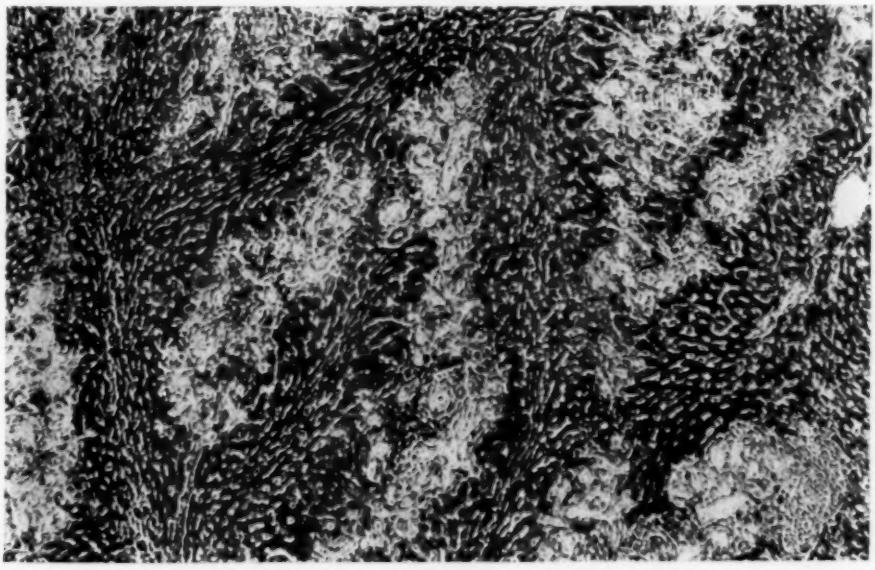

Fig. 3.—Biliary cirrhosis in liver of white rat twenty-one days after ligation of bile duct; × 90.

revealed considerable iron within hepatic cells around these yellow-tinged bile deposits.

Besides the necrotic changes that occurred in the lobule, and the increase in local histiocytes, there was portal infiltration by lymphocytes and polymorphonuclear leukocytes. Marked distention of the extrahepatic bile duct proximal to the ligature occurred, but the intrahepatic ducts were also enlarged. Extensive pericholangitis developed around the proliferated newly formed bile ducts and ultimately formed wide zones of fibrous tissue around the reduced areas of functioning parenchyma (fig. 3). A study of the sections gave no evidence, however, that true hepatic restoration had occurred. The rapid increase in the size of the hepatic remnant following partial removal in any animal is probably associated with hypertrophy of the

hepatic cell and karyokinesis. Certainly by far the greatest increment is attained by an increase in the size of the preexisting cells, for cell division, although frequent during the second and third day, is not sufficient to produce so rapid an increase in weight. In the presence of biliary obstruction, these two cell reactions did not occur to any extent. Occasional mitotic figures were seen, and certainly the cellular hypertrophy which did occur was not comparable to that which ensues on partial removal, but more likely is due to factors associated with pressure induced by the intracellular retention of large quantities of inspissated bile.

The large ratios of weight of liver to weight of body that were recorded during the first, second and third weeks of this experiment are thus explained not as true restoration, such as ensues on partial removal alone, but as a result of actual distention of the lobules of the liver with constituents of bile and erythrocytes.

COMMENT AND SUMMARY

These experimental results, although differing somewhat from those of Mann, Fishback, Gay and Green,[2] rather definitely support their conclusion that restoration of the liver following partial removal does not take place extensively in the presence of biliary obstruction. They induced obstruction by ligation of the common bile duct in dogs at about thirty days before partial hepatectomy, whereas we combined removal with ligation in a single operation. In their study, restoration was induced long after the effects of obstruction had been imposed; in our study, the factors of restoration were operative coincidentally with the effects of obstruction to biliary outflow.

As far as size and weight of the liver are concerned, the results of partial hepatectomy in the presence of obstruction are not dissimilar to those of true restoration. Ligation of the duct induced in dogs, as it did in white rats, a greenish-brown organ, greatly distended and engorged. This engorgement with inspissated bile explains, we believe, the increased ratios of weight of liver to weight of body that were recorded and plotted in curve *c* of figure 1. Accordingly, from the weight of the organ alone one may not predict the extent of acutal restoration following removal that occurs in the presence of total obstruction. When hepatectomy was performed in the presence of biliary obstruction, a certain amount of hepatic restoration no doubt occurred before the distention, induced by the obstruction, interfered. The occasional mitotic figures noted on the second day, indicated that at least some restoration had taken place. Mitotic division was not observed in hepatic cells during the later periods of obstruction when large globules of bile had so distorted the cell as to dislodge the nucleus to an eccentric position.

The rapid rate of restoration that occurs in normal rats during the first two or three days following partial removal seems to be largely correlated with the volume of blood traversing the liver. In fact, observations now in progress in this laboratory lead us rather definitely to conclude that the entire principle of restoration following removal is definitely correlated with the amount of blood passing through the remaining portion of parenchyma after removal. Stephenson [4] showed that when the portal vein of the rat is partially ligated so as to restrict the volume of blood entering the liver, the extent of restoration following removal is greatly reduced. We have noted always marked congestion of the remnant of the liver the first few days after the removal of the usual 70 per cent component. The sinusoids distend in order to make a capillary bed available that is adequate to handle the preoperative portal blood volume. This distention we believe induces coincident hypertrophy of the hepatic cell which, with the occasional mitosis, may largely explain all that is involved in hepatic restoration.

In the presence of obstruction, however, the marked distention of the sinusoids of the remnant of organ, following removal of the 70 per cent component, did not occur. In some cases, the sinusoids were open and, of course, circulation through the glands ensued, but the rather marked congestion during these early hours following operation was not observed in animals with biliary stasis. This, we feel, is largely due to the distention of the hepatic cells with bile, encroaching somewhat on the sinusoids and impeding the flow of the usual volume of blood.

The changes in the liver that occurred during the fourth week, as determined by the loss of weight as well as by histologic section, are of interest (fig. 1 *b*). If the animals that survived and were killed on the twenty-eighth day after operation had experienced the same hepatic changes as those that were killed up to the end of the third week, and there is every reason to believe that they had, for jaundice of sclera, mucous membranes and urine were well marked, then, with the reestablishment of a patent bile duct, the retained constituents of the bile were removed, and the liver became more nearly normal. Under these conditions, then, the ratios of weight of liver to weight of body recorded at twenty-eight days were not only greatly lower than those at twenty-one days, but they were considerably lower than those describing the extent of restoration in the control animals (fig. 1 *a*).

On the basis of these observations we were led to believe that in the presence of obstruction to the bile duct in white rats, true restoration following the removal of about 70 per cent of the liver is not as marked as in animals in which the bile duct remains intact.

4. Stephenson, G. W.: Arch. Path., to be published.

MECONIUM PERITONITIS

II. A HITHERTO UNDESCRIBED FORM OF INTRA-UTERINE PERFORATION OF A MECKEL'S DIVERTICULUM

W. S. BOIKAN, M.D.
CHICAGO

In a recent review of the etiology and pathology of meconium peritonitis, I [1] brought forth a hitherto undescribed cause for spontaneous intra-uterine perforation of the terminal ileum. In a new-born, full-term infant who died twenty-six hours post partum with fever and abdominal distention there was found post mortem an old, fibrous, calcified body meconium peritonitis, on which was superimposed a recent bacterial inflammation. As the cause of both there was present a small perforation in the antimesenteric side of the terminal ileum. Serial sections through the segment of bowel bearing the perforation revealed excessive development of the lymphoid tissue of a Peyer's patch in the bowel adjacent to the perforation, with the presence of deep, penetrating crypts of Lieberkühn in the lymphoid tissue. The sections through the perforation itself showed this same lymphoid tissue with its deeply invading glands becoming so massive as to cause gradual thinning of the muscularis, which at the perforation completely disappeared, so that the tissue reflected about the opening was composed only of lymphoid tissue and mucosa.

It was conceived that in the pathogenesis the deeply invading crypts of Lieberkühn were derived from the antimesenteric diverticula described by Lewis and Thyng [2] as occurring in pig, rabbit and human embryos at 5 to 32 mm. Generally these diverticula disappear, but investigators [3] have shown their occasional normal occurrence in a wide range of animals, including human fetuses and children, as deep intra-lymphoid crypts of Lieberkühn in the terminal ileum, appendix and even colon.

Since these diverticula occur in 5 to 32 mm. embryos, and since the lymphatic tissue does not develop until the embryo reaches a length

From the Department of Pathology, Cook County Hospital, Dr. R. H. Jaffe, director.

1. Boikan, W. S.: Arch. Path. **9**:1164, 1930.

2. Lewis, F. T., and Thyng, F. W.: Am. J. Anat. **7**:505, 1907-1908.

3. Lauche, A.: Virchows Arch. f. path. Anat. **252**:39, 1924. Klaatsch, cited by Lauche. Lubarsch, O., cited by Lauche. Meyer, R.: Verhandl. d. deutsch. path. Gesellsch. **10**:216, 1906. Orth, J.: ibid. **3**:135, 1901.

of from 240 to 300 mm., the excessive lymphoid hyperplasia was considered as a reaction to these persistent diverticula. The atrophy of the muscularis was considered secondary to the overdevelopment of the lymphoid tissue. The rupture occurred with the development of a positive intra-intestinal pressure associated with the arrival of the meconium in the lower part of the ileum at about the middle of the fourth month.

It was therefore of great interest when in the study of a second case of meconium peritonitis there was found an identical mechanism, operative, however, this time in a Meckel's diverticulum.

In addition, interesting aspects of fetal physiology and pathology were uncovered. It appeared therefore justifiable to report the study of this second case of meconium peritonitis.

REPORT OF A CASE

History.—The child was a well developed, colored boy delivered normally and spontaneously. The mother was a young colored multipara, who had received long and intense treatment for syphilis.

At birth, herniation was noticed in the umbilical region. As its condition seemed good, surgical intervention was deemed unnecessary. At the first redressing of the cord, a discharge of meconium was noted about the umbilical defect. Twenty-four hours after delivery, the abdomen appeared distended, and there had occurred no movement of the bowels; fifty-one hours after delivery, the child died.

Postmortem Examination (Dr. R. H. Jaffé).—A well developed, colored, male infant, dead two hours, was presented. The skin was icteric. The anterior, posterior and mastoid fontanels were open. The pupils were equal and regular; the conjunctivae, icteric. The breasts were engorged; the abdomen was distended 1 fingerbreadth above the level of the thorax. The testicles were in the scrotum. There were collodion-sealed needle wounds at the inner aspect of the thighs, just above the knees. Attached to the right little finger was a pedunculated structure, 11 by 5 by 6 mm., which resembled a terminal phalanx. On the left little finger, in the same position, was a wartlike structure 1 mm. in diameter. In the region of the umbilicus, there was a defect, 15 mm. long and 5 mm. wide. Through this defect, the umbilical vein and the hypogastric arteries herniated. The umbilical vein was thickened up to 8 mm. and covered by dirty, greenish-gray, fibrinous exudate. The hypogastric arteries were similarly thickened up to 6 mm. and also covered by fibrinous material. In the most distal portion of the vein, the lumen was occluded by a slightly adherent, reddish-gray thrombus. The hypogastric arteries were similarly occluded.

The abdominal cavity contained about 30 cc. of yellowish-green, cloudy fluid. The intestinal loops were all matted together and enveloped in thin, fibrinous exudate. Projecting through this fibrinous wall, in the right lower quadrant, was an elevated, buttonlike nodule with everted edges, composed of injected mucosa, in the central portion of which was an ostium, 1 mm. in diameter, from which yellowish-green fecal material exuded. On separating the intestinal loops, it was found that this ostium was situated in the ileum 6 mm. above the ileocecal valve on the antimesenteric border. Opposite the perforation, the bowel became small, measuring 3 mm. in diameter as compared with the 9 mm. diameter of the ileum above the perforation. In the 2.5 cm. between the perforation and the cecum, the ileum

widened gradually to 5 mm. The colon, which was tightly contracted, measured 5 mm. in diameter, and was therefore only a little over one half of the diameter of the normal-sized ileum. This fact is of importance, as it casts a light on the time of the perforation and on the physiologic factors that determined the development of the bowel. The rectum at its anal end suddenly widened to 8 mm. The lumen was patent throughout. Meconium was present in the bowel only above the perforation. Distal to the perforation, only grayish, thick material was found.

The diaphragm over the right dome of the liver presented an area 3 cm. in diameter through which a corresponding node of the liver was herniated. The sac of the hernia did not contain muscle tissue from the diaphragm, but was composed of peritoneum and pleura. Smaller herniations of a similar character (up to 1 cm. in diameter) were found adjacent to the larger one, but did not contain hepatic tissue.

The spleen weighed 25 Gm., was soft and deep purple.

The liver weighed 210 Gm.; the surface was covered by thick, fibrinous exudate. The consistency was soft. The section surface was greenish brown, with the markings obscured. The gallbladder and ducts were normal.

The pancreas weighed 4 Gm.; the duct was patent.

The suprarenal glands weighed 18 Gm.

The kidneys weighed 40 Gm. The surfaces were smooth. The right kidney had a double ureter that formed a common duct 1 cm. above the bladder. Numerous uric acid infarcts were observed in the pyramids. The wall of the urinary bladder was edematous. There was slight injection about the trigon.

The lungs were covered by rather adherent, fibrinous exudate. The section surface was pinkish gray throughout.

The pericardial cavity contained a little clear fluid. The heart weighed 35 Gm.; the foramen ovale was patent.

Anatomic Diagnosis.—Meconium peritonitis with terminal secondary bacterial peritonitis; defect in the lower part of the ileum, on the antimesenteric border, communicating with the abdominal cavity; hypoplasia of the ileum and colon distal to the perforation; herniation of a portion of the liver through the diaphragm and of the umbilical veins and hypogastric arteries through the abdominal wall; patent foreman ovale and ductus venosus; pseudopolydactylism.

Microscopic Examination.—Sections were made of all the organs. In addition, the entire intestinal tract was sectioned at short intervals. The segment of terminal ileum bearing the perforation was sectioned transversely, each section being 6 microns' thickness and every third section stained. As normal control there served the serial sections through the entire intestine prepared previously from three newborn infants who died of cerebral injuries. Hematoxylin-eosin stains were used throughout.

The sections of all the organs other than the intestines revealed no abnormality other than microscopic corroboration of the presence of meconium peritonitis. There was no gross or microscopic evidence of syphilis in cutaneous, visceral or osseous organs. Adherent to the mesenteries and serous surfaces of all the abdominal organs was a thick layer of a partially organized admixture of meconium and fibrin, infiltrated with numerous macrophages filled with golden-brown pigment, foreign body giant cells, fibroblasts and round cells, and containing numerous free brown and blue granules and clumps. Numerous polymorphonuclear leukocytes were an evidence of the recent acute bacterial inflammation.

The jejunum and ileum presented no abnormalities. The lymphoid follicles were small, and the muscle gaps produced by the entrance of blood vessels were small. The mesenteric vessels were normal.

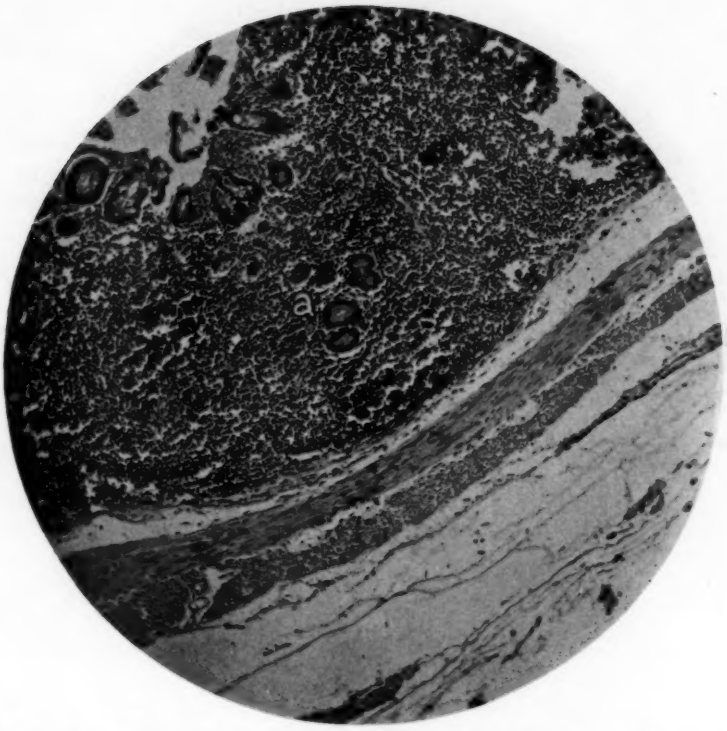

Fig. 1 (level fig. 5 *B-1*).—The section was made through a Peyer's patch. Note the glands of Lieberkühn deep within the lymphoid tissue in the submucosa (*a*); hematoxylin-eosin; × 72.

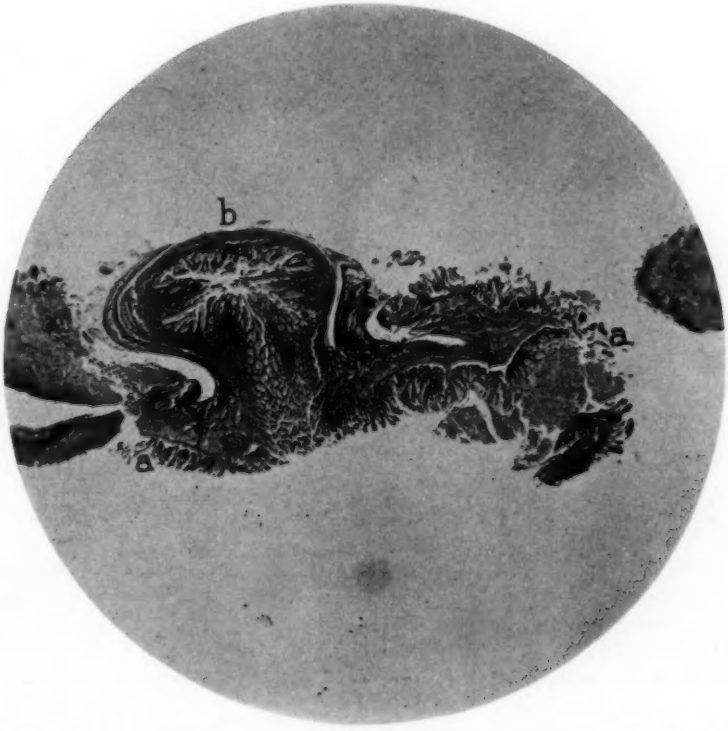

Fig. 2 (level fig. 5 *B-2*).—This section through the perforation shows the large everted walls of the ruptured diverticulum (*a*); hematoxylin-eosin; × 10. At *b* there was an accidental removal of mesentery and muscularis at autopsy.

Fig. 3 (level fig. 5 *B-3*).—This section shows the huge size of the inferior flap at *a;* in comparison with the total bowel at this level (*b*); hematoxylin-eosin; × 10.

Fig. 4 (fig. 5 *B-4*).—This section through the distal half of the reflected inferior flap shows the absence of muscularis and the large amount of lymphatic tissue (*a*) and deeply penetrating crypts of Lieberkühn (*b*); hematoxylin-eosin; × 70.

The ileum, immediately above the perforation, presented a significant feature (fig. 1; fig. 5 *B-1*). The section was made through a Peyer's patch. The lymphatic tissue composing it extended down to the muscularis and laterally in the submucosa for a considerable extent. The muscularis mucosa was interrupted for the extent of the Peyer's patch, and the crypts of Lieberkühn protruded deep into the lymphoid tissue, to within a short distance of the muscularis. The muscularis was not particularly narrowed in the region of the Peyer's patch. This finding parallels that found in the previous case that I described.[1]

Serial transverse sections through the perforation itself revealed the following: As one approached the perforation, it appeared suddenly on the antimesenteric side and without any upward extrusion of a flap. The bowel at this point diminished suddenly to about one third its size above the perforation. As the serial sections were followed down, two large lateral flaps appeared, which were composed of all the layers of the intestinal wall and were so rolled out as to be completely covered by epithelium. It soon became apparent that the total length of the flaps exceeded

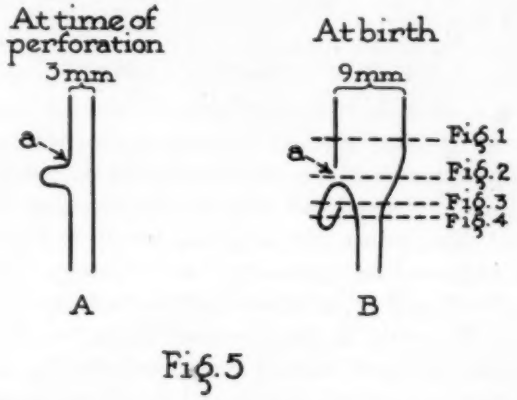

Fig. 5

Fig. 5.—Diagram showing in *A* the diameters of the terminal ileum and the intact diverticulum just preceding perforation, and in *B*, the diameters at time of birth, demonstrating the ruptured diverticulum, the normal development of the proximal (9 mm.) seg . and the hypoplasia of the distal segment. The transverse lines refer to the levels from which the sections shown in the preceding four figures were obtained.

the circumference of the segment of bowel from which they arose, a fact incompatible with any conception other than that one was here dealing with the everted walls of a diverticulum, which because of location and position was most likely Meckel's diverticulum (fig. 2; fig. 5 *B-2*). These flaps became progressively larger until at the inferior margin of the perforation they formed a flap that had a width of 7 mm. as compared with the diameter of 3 mm. of the adjacent bowel (fig. 3; fig. 5 *B-3*). Furthermore, this flap was almost completely everted and rolled on itself so as to be completely covered by epithelium, rendering its width at least twice that heretofore mentioned. This inferior flap was tongue-shaped and extended far down alongside the terminal ileum for over 3 mm. At its origin, this inferior flap contained all the layers of the intestinal wall. In its lower two thirds, however, the muscularis rapidly thinned and disappeared, leaving the distal one half of the flap composed of mucosa and submucosa. The latter contained a large amount

of lymphatic tissue and was deeply penetrated by intralymphoid glands of Lieberkühn (fig. 4; fig. 5*B-4*). The blood vessels of the flap were widely dilated and filled with blood. In its lower one third, the flap ended tonguelike and was composed of a huge Peyer's patch completely surrounded by mucosa and containing invading Lieberkühn glands.

The epithelium of the diverticulum was of the normal intestinal type. Cystic glands were frequent and were probably of inflammatory origin, from the chemical inflammation in the peritoneum.

Within the segment of the perforation, the bowel was perfectly normal in all respects except for its small size. Distal to the perforation, the ileum was similarly histologically normal with the exception of its small size. It represented, as it were, a bowel uniformly and symmetrically checked in its development. Within the lumen were some shed epithelial cells and irregular débris, but no pigment.

The entire colon formed a 5 mm.-wide, tightly contracted tube—a little more than one half the size of the small intestine. The component layers were histologically normal. The lumen contained a little poorly stained débris and a few cast-off epithelial cells.

SUMMARY OF ESSENTIAL FINDINGS

In addition to chronic meconium peritonitis with calcification and fibrosis and recent superimposed acute bacterial inflammation, the essential findings consisted of: A perforation in the antimesenteric side of the ileum, 2.5 cm. from the cecum, bounded by lateral and inferior everted flaps, which far exceeded the size of the perforation and therefore suggested the presence of a perforated, everted Meckel's diverticulum. The lateral flaps consisted of all the layers of the intestinal wall; the lower flap, only in its upper one half, the distal half being composed almost entirely of mucosa and submucosa, the latter occupied by a large amount of lymphatic tissue and deeply penetrating crypts of Lieberkühn. In the ileum, just above the perforation, a Peyer's patch contained Lieberkühn's crypts. Finally, distal to the perforation, the entire bowel was markedly hypoplastic, so that the colon was a little over one-half the size of the small intestine and contained no meconium,

COMMENT

The rôle of Meckel's diverticulum in the causation of acute and chronic pathologic abdominal conditions at all stages of intra-uterine and extra-uterine life has been adequately discussed by numerous authors.[4] Meckel's diverticulum is a common cause of fetal intestinal obstruction. Few reports exist as to its spontaneous fetal rupture and

4. Halstead, A. E.: Ann. Surg. **35**:471, 1902. Koch, W., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 4, pt. 1, p. 175. Siegmund, H.: ibid., vol. 4, pt. 3, p. 94. Evans, A.: Brit. J. Surg. **12**:34, 1929. Christie, A.: Am. J. Dis. Child. **42**:544, 1931.

causation of meconium peritonitis. Hunter [5] recently reported gangrene of a Meckel's diverticulum with perforation peritonitis in an infant 4 days old. The cause of the gangrene was considered circulatory. A similar case was reported by Shukowski.[6] Early fetal rupture was described by Genersich [7] and by Orth.[8] In neither case was the histopathogenesis discussed. In analyzing the present case, two questions arise: When did the perforation occur? Why did it occur? They will be discussed in this order.

Time of Perforation.—As stated, distal to the perforation the ileum was about one-third the size of the normal intestine above the perforation, and the colon had a diameter of 5 mm. in comparison with the diameter of 9 mm. of the ileum. Now, in its development, the large intestine is for a long time narrower than the small intestine. This is the case even before there is any intestinal content, that is, at about the end of the third month. But the small intestine becomes still wider relatively when, early in the fourth embryonic month, hepatic secretion and formation of meconium commence. Meconium, according to Broman,[9] distends and stimulates the intestine to growth, and its progressive downward propulsion by fetal peristalsis is a most important factor in the proper development of the bowel. At about the end of the fourth month, meconium enters the cecum, and the continuous storage of this material in the large bowel leads to rapid growth of the colon, so that it equals the small intestine in diameter by the seventh or eighth month and then rapidly exceeds it.

The appendix does not take part in this growth, because a valve-like fold of mucosa protects it from the entrance of meconium.

As proof of this conception, Broman cited the stringlike character of the intestine distal to an adhesion. Further, he pointed out that an anomalous communication of the small intestine or cecum that diverts the meconium is almost regularly associated with atresia of the rectum. The latter is, however, untenable, as the anal groove breaks through into the rectum when the embryo is 30 mm., and meconium is not secreted until the embryo is between 90 and 100 mm. This is further borne out in the present case by the absence of any rectal or anal anomalies despite the diversion of meconium. But that meconium does stimulate the development of the bowel is shown in this case, in which diversion of the meconium by the perforation in the lower part of the ileum led to

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5. Hunter, W. C.: Am. J. Dis. Child. **35**:438, 1928.
6. Cited by Hunter (footnote 5).
7. Genersich, A.: Virchows Arch. f. path. Anat. **126**:485, 1891.
8. Cited by Genersich (footote 7).
9. Broman, I.: Normale und abnormale Entwicklung des Menschen, Wiesbaden, J. F. Bergmann, 1911, p. 344.

marked hypoplasia of the ileum and colon distal to the perforation. Even postnatal gastro-intestinal development is dependent on similar factors. The recent observations of Addis [10] as well as those of others point to an intimate relationship between the length, caliber and weight of the various segments of the gastro-intestinal tract and the character of the contents. He could demonstrate marked changes in rats after forty-four days of a diet high in roughage; the stomach increased 35 per cent in weight, and the colon 48 per cent in weight and 34 per cent in length, with smaller changes in the small intestine. Since observations (Mall [11]) indicate that meconium reaches the cecum at about the fourth month, and since the bowel distal to the perforation contained no meconium, it places the act of perforation at a period near the end of the fourth month.

Mechanism of Perforation.—It became obvious that this was a perforated Meckel's diverticulum when it was noted that the flaps about the perforation, when reconstructed, exceeded the size of the diminutive ileum at this point. The perforation of the diverticulum at about the end of the fourth month had diverted the meconium, and the entire bowel distal to the perforation had then ceased to develop.

The etiology of the perforation is to be seen in the serial study of the lower flap, which showed rapid disappearance of the muscle layers, as described in a foregoing paragraph concomitant with the submucosal development of a large amount of lymphatic tissue containing deeply penetrating crypts of Lieberkühn. In its distal third, the flap was composed only of a mass of lymphatic tissue.

In figure 5, *A* represents the bowel and the diverticulum at about the time just before the perforation. *B* represents the bowel as found at autopsy, showing the perforation and the lower flap, the inhibited development of the bowel below the perforation with retention of the same diameter as in *A*, and the normal development of the meconium-filled bowel above the perforation. In *A*, the point marked *a* corresponds to the part of the flap depicted in figure 4. This was a locus of diminished resistance to intra-intestinal pressure, and when the latter became positive by the entrance of meconium, it perforated, causing an eversion of the diverticulum and the formation of the lateral and inferior flaps (fig. 5 *B*).

The thinning and gradual disappearance of the muscularis in the wall of the diverticulum are attributed, as in my previous case, to the excessive development of the lymphatic tissue in the submucosa in association with the deep submucosal intralymphatic crypts of Lieberkühn.

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10. Addis, T.: Am. J. Physiol. **99**:417, 1932.

11. Mall, F. P., in Keibel and Mall: Human Embryology, Philadelphia, J. B. Lippincott Company, 1912, p. 390.

Why this association of excessive development of the lymphatic tissue with intralymphatic crypts of Lieberkühn is not a constant one, —that is, why the latter may be present without excessive development of lymphatic tissue cannot be answered at present, except that in these instances the glands are larger and deeper than in those segments in which there is no excessive lymphoid hyperplasia. Evidence of lymphoid hyperplasia elsewhere in the body was lacking. The distention of the abdomen from the chemical peritonitis was no doubt a factor in the production of the umbilical herniation. The terminal bacterial peritonitis and pleurisy were no doubt of postnatal origin from postnatal bacterial emigration through the intestinal perforation.

SUMMARY

A case of meconium peritonitis from spontaneous intra-uterine rupture of a Meckel's diverticulum in the first half of intra-uterine life is described.

The cause of the rupture was the excessive development of lymphatic tissue in association with deep submucosal crypts of Lieberkühn in the wall of the diverticulum, with secondary focal disappearance of muscularis. Rupture took place with the development of positive intra-intestinal pressure from the entrance of meconium.

The short segment of ileum and the entire colon distal to the perforation were hypoplastic and devoid of contents, the colon retaining its early fetal proportion to the small intestine. This is attributed to the lack of the distending and growth-stimulating action of the meconium, diverted by the perforation into the peritoneal cavity.

3815 West End Avenue.

ACTION OF PARATHYROID HORMONE ON THE EPIPHYSEAL JUNCTION OF THE YOUNG RAT

HANS SELYE, DR. RERUM NAT., M.D.
BALTIMORE

After Collip described his method for the preparation of highly active parathyroid extracts, many investigations were undertaken to determine the effect of high doses of such extracts. Definite changes were described as occurring when large amounts of parathyroid hormone were administered. These form the pathologic entity of hyperparathyroidism. Furthermore, it has been demonstrated that changes similar to those produced experimentally in animals are found in human subjects in whom a pathologic overfunctioning of the parathyroid glands exists (e. g., hypertrophy or adenoma of the parathyroid glands).

The most striking morphologic effect produced by excessive amounts of parathyroid extracts is the deposition of calcium salts in the soft tissues, such as the kidneys, the heart muscle, the mucous membrane of the stomach, etc. Experimental work has been reported adequately describing these changes in rats [1] and in dogs.[2] That such metastatic calcification may also occur in human subjects as the result of hyperparathyroidism has been shown in a case of parathyroid adenoma combined with general organic calcification which I described.[3]

While hyperparathyroidism leads to a deposition of large amounts of calcium in the tissues, the calcium content of the bones is diminished. An active resorption of bone tissue occurs, and the skeleton becomes weak and brittle, so that numerous spontaneous fractures occur. At the same time, the marrow is transformed into fibrous tissue, so that the changes are very similar to those observed in osteitis fibrosa (von Recklinghausen). This condition is also related to hyperparathyroidism as shown by experiments [4] and observations in man.[5]

From the Department of Chemical Hygiene, School of Hygiene and Public Health, Johns Hopkins University.

1. Hoff, F., and Homann, E.: Ztschr. f. d. ges. exper. Med. **74**:259, 1930.

2. Jaffe, H.; Bodansky, A., and Blair, J. E.: Klin. Wchnschr. **9**:1717, 1930. Bodansky, A., and Jaffe, H. L.: J. Exper. Med. **53**:591, 1931. Jaffe, H. L., and Bodansky, A.: Proc. Soc. Exper. Biol. & Med. **27**:795, 1930.

3. Selye, H.: Med. Klin. **25**:379, 1929.

4. Jaffe, H. L.; Bodansky, A., and Blair, J. E.: Proc. Soc. Exper. Biol. & Med. **27**:710, 1930; **28**:793, 1931; Arch. Path. **11**:207, 1931.

5. Hunter, D.: Proc. Roy. Soc. Med. **24**:486, 1931. Snapper, I.: Nederl. tijdschr. v. geneesk. **2**:5804, 1929. Stearns, J., and Boyd, J. D.: Proc. Soc. Exper. Biol. & Med. **26**:717, 1929.

Effects very similar to those produced by parathyroid extracts are also produced by viosterol, the toxicology of which has been studied by many workers during the last few years. This substance likewise leads to metastatic calcification of the soft tissues when given in large doses (Kreitmair and Moll). If large amounts of viosterol are fed to very young animals, spontaneous fractures occur. The rapid skeletal growth of immature animals renders them especially fit for such experiments. Thus I [6] demonstrated that the offspring of rats receiving large amounts of viosterol during the latter half of pregnancy, or only during lactation, show a severe form of osteopsathyrosis, with cessation of growth and numerous spontaneous fractures. These experiments and the later work of others [7] indicate that viosterol can pass through both the placenta and the mammary glands. In somewhat older rats, striking changes in the epiphyseal junctions are produced by an overdosage of viosterol. The zone of cartilage cell columns in these animals is short, and the ground substance between these cells is excessively impregnated with calcium. In adult animals, the changes are not so striking and vary with the diet used.[8]

In their effects on coagulation of the blood, the parathyroid hormone and viosterol have also proved to be closely related. Ample evidence exists to show that both shorten the period necessary for coagulation of the blood.[9]

The similarity of the effects of the viosterol and the parathyroid hormone is striking. In fact, Taylor and his co-workers [10] suggested that viosterol in large doses acts through the parathyroid glands.

The experiments cited show that the bones of very young animals are much more sensitive to the toxic action of viosterol than are those of older animals. Hence it is of some interest to determine the effect of an overdosage of parathyroid hormone on the bones of young rats during the suckling period.

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6. Selye, H.: Krankheitsforschung **7**:289, 1929; Med. Klin. **24**:1197, 1928.

7. Camel, M.: Boll. d. Soc. ital. di biol. sper. **5**:738, 1930. Schoenholz, L.: Klin. Wchnschr. **8**:1257, 1929.

8. Schmidtmann, M.: Virchows Arch. f. path. Anat. **280**:1, 1931.

9. Selye, H.: Klin. Wchnschr. **7**:1891, 1928. Phillips, R. A., and Robertson, D. F.: Proc. Soc. Exper. Biol. & Med. **26**:639, 1929. Corson, W. C.; Irwin, G. F., and Phillips, R. A.: ibid. **27**:488, 1930. Phillips, R. A.; Robertson, D. F.; Corson, W. C., and Irwin, G. F.: Ann. Int. Med. **4**:1134, 1931. Braugher: Northwest Med. **29**:38, 1930. Ohshima, Shiro: Mitt. d. med. Gesellsch. zu Tokio **43**:115, 1929.

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EXPERIMENTS

Litters of 10 day old rats were used for these experiments. Half of the young rats were treated with parathormone,[11] and the others were retained as controls. Parathormone was administered intraperitoneally, 5 units for each rat daily for three days. The dose was then increased to 10 units daily. The little rats, weighing about 15 Gm. each, tolerated this high dosage relatively well. On the other hand, adult rats given 10 units daily for each 15 Gm. of body weight died within a few days, showing general metastatic calcification. The growth of the young rats treated with parathormone was arrested. About the sixth day of

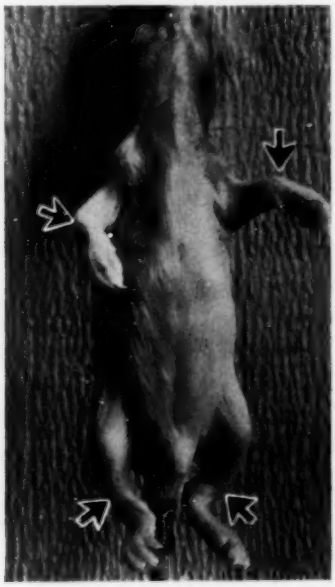

Fig. 1.—Arrows show points of bending.

the administration of parathormone, a marked deformation of the skeleton became apparent. The diaphyses of the long tubular bones were straight; in the epiphyseal region, however, severe bowing was readily observable. Further treatment resulted in aggravation of these symptoms. The condition produced is illustrated in figure 1.

At autopsy, the bones of these animals were soft and easily cut with a scalpel. The process of ossification of the cartilaginously preformed bones was retarded. While the epiphyses of the normal litter mates were normally ossified almost throughout the whole extent, the ossification centers in the animals treated with parathormone were represented by

11. The parathormone used in these experiments was provided by Eli Lilly & Company.

only a small area of bone tissue in the center of the cartilaginous epiphyses. The cartilage of the epiphyseal junction was irregular. Shaftward of this cartilage, a red hyperemic line could be seen, and under this a zone of rather dense but soft tissue was visible. It was in this zone that the bending of the bones occurred. The marrow was usually red, but in two cases a pale yellow marrow was found. The calvaria was so thin that only a transparent soft membrane was present. Metastatic calcification in soft tissues occurred only to a limited extent.

Histologically (see figs. 2 and 3), only sections not decalcified were examined. In these, the broad and irregular epiphyseal cartilage was of a pale color in its ground substance. In the zone of provisional calcification, no deposition of calcium could be found in the ground substance in contrast to the findings in the untreated litter mates. There was marked hyperemia in the zone of primary marrow formation corresponding to the red line that was seen macroscopically. Below this line, practically the whole bone consisted of distinctly eosinophilic osteoid tissue. The formation of soft osteoid tissue to so large an extent in this zone seems also to be responsible for the fact that the bones invariably became bent in the region of the epiphyseal junction. The cortex of the bones was thin, and at the point of bending the periosteum invaded the marrow cavity, and there developed a fibrous marrow. In the other parts, however, the bone marrow was chiefly of the lymphoid type.

These findings are especially interesting in connection with the work of Lang [12] and others who, in opposition to Christeller and others,[13] expressed the belief that osteitis fibrosa is only a secondary process, which may occur whenever the bone is so decalcified that the circulation within the bone marrow is subjected to alterations in consequence of mechanical injuries. They also found a close relationship between rickets, osteomalacia and osteitis fibrosa and called attention to the fact that fibrous metaplasia of the marrow occurs also in many cases of human rickets and osteomalacia. In our experiments, the effect of mechanical influences in the production of fibrous marrow was clearly demonstrated, as the fibrous metaplasia always occurred in those areas subjected most to mechanical strain (sites of bending).

The striking changes that are apparent at the epiphyseal junctions as a result of large doses of parathormone, namely, the broad, irregular cartilage, the lack of a deposition of calcium in the zone of provisional

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12. Lang, F. J.: Klin. Wchnschr. **5**:228, 1926; Virchows Arch. f. path. Anat. **257**:594, 1925; Beitr. z. path. Anat. u. z. allg. Path. **87**:143, 1931. Lang, F. J., and Häupl, K.: Virchows Arch. f. path. Anat. **262**:383, 1926.

13. Christeller, E.: Verhandl. d. deutsch. path. Gesellsch. **21**:7, 1926. Schmorl, G.: Klin. Wchnschr. **5**:496, 1926. Stenholm, T.: Pathologisch-anatomische Studien über die Osteodystrophia Fibrosa, Upsala, 1926.

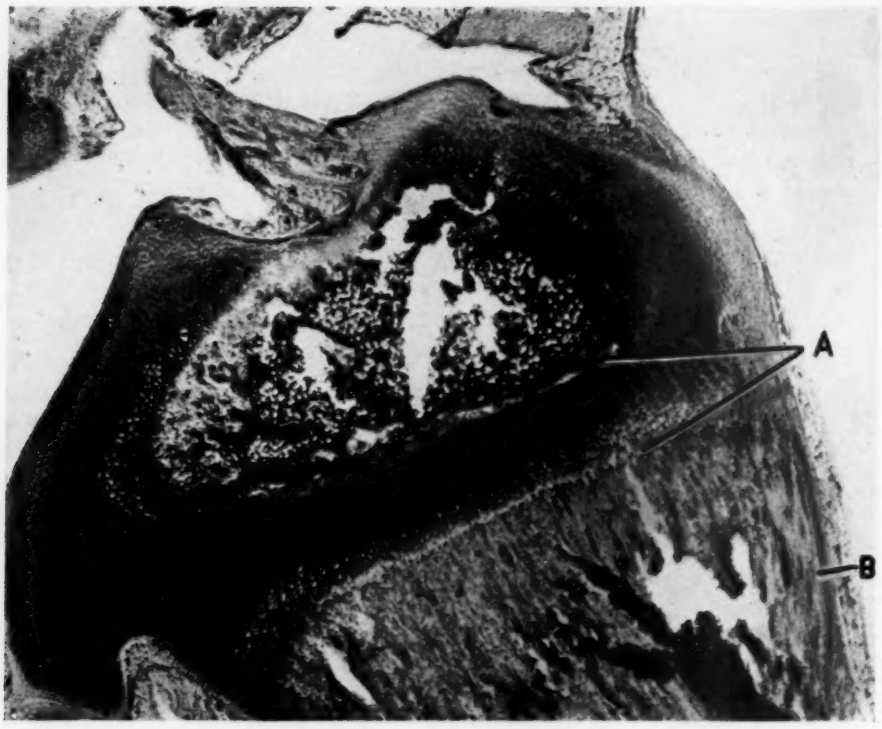

Fig. 2.—Normal epiphysis of the control animal: *A*, narrow, regular junction cartilage; *B*, normal bone tissue.

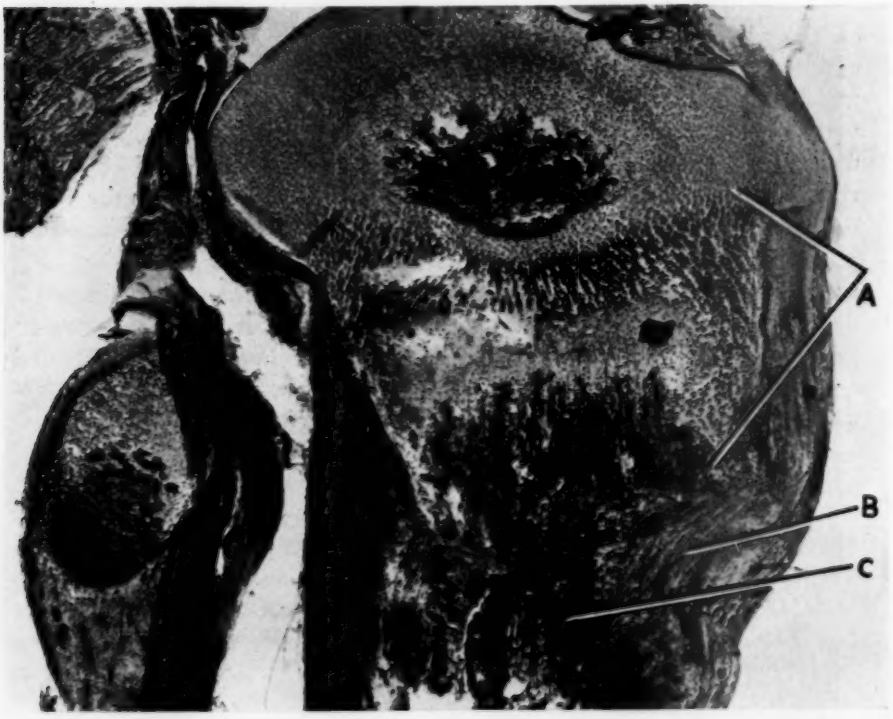

Fig. 3.—Epiphysis of a parathormone-treated litter mate of the animal represented in figure 2. *A*, enlarged, irregular junction cartilage without any trace of a deposition of calcium in the zone of provisional calcification; *B*, osteoid bone tissue; *C*, fibrous marrow.

calcification and the formation of excess osteoid, especially in the region of the cartilage junctions, lead one to view these changes as suggestive of those seen in severe forms of rickets.

Although these changes following the administration of parathormone are suggestive of rickets produced by dietary means, no conclusion as to whether or not the two lesions can be considered identical is possible until further experimental and histologic work now under way is completed.

SUMMARY

Young rats are more resistant to an overdosage of parathyroid extract than adult rats. Even when fatal doses of parathormone are administered to lactating rats, extensive metastatic calcification does not occur, as is invariably the rule in adults.

On the other hand, the bony system of young rats is readily and seriously damaged by large doses of parathormone, and the changes so produced are most striking in the region of the epiphyseal junctions in the so-called growth zones. There the changes are *suggestive of severe rickets.*

The fibrous metaplasia of the bone marrow occurs almost exclusively in those areas where severe mechanical strain exists (points of bending of the bones). This corroborates the theory that osteitis fibrosa is not a primary disease of the bone, a pathologic entity, but a secondary effect of mechanical injury to the circulation within the weakened bone, quite independent of the cause of this weakening. Therefore it would appear to be *incorrect to consider osteitis fibrosa simply as a specific effect of hyperparathyroidism.* The occurrence of osteitis fibrosa in the course of experimental scurvy [14] likewise substantiates this view.

The theory that viosterol acts through the medium of the parathyroid glands is not confirmed by these experiments, as the disease produced by hyperparathyroidism in young rats described in this paper, markedly differs from that produced under the same conditions by the so-called "hypervitaminosis D."

14. Bauer, W.: Beitr. z. path. Anat. u. z. allg. Path. **87**:23, 1931.

EXPERIMENTAL PRODUCTION OF GALLSTONES

WITH A REVIEW OF THE LITERATURE

CORNELIUS A. HOSPERS, PH.D.
CHICAGO

The origin of biliary concretions is still a disputed question. One avenue of information lies in the experimental production of calculi, and numerous attempts have been made to produce them.

Blachstein [1] (1891) injected B. coli and B. typhosus intravenously into rabbits, and found that those living from eight to one hundred and nine days "usually" contained in the gallbladder opaque yellowish particles consisting of epithelial cells, leukocytes, amorphous masses of bile pigment and clumps of bacteria. He could detect no differences between the effects of B. coli and those of B. typhosus. Welch [2] could not find these particles in the gallbladder of a rabbit four months after injection of B. typhosus.

Marcantonio [3] reported that he infected a dog's gallbladder, but found no formation of calculus after six months. Injection of lactic acid into the gallbladder of a dog gave negative results. He succeeded in producing a kind of gallstone, however, by deposition of pigment calcium on a foreign body placed in the gallbladder of a dog. This deposit contained no cholesterol.

Gilbert and Dominici [4] produced cholecystitis in a rabbit by intravesical injection of B. typhosus and found a small concretion in the gallbladder.

Mayer [5] placed pieces of ivory, clay balls and bits of agar in the gallbladders of dogs. After one year, the agar had disappeared, but the solid bodies in some cases had been covered with a thin layer of green-brown or black-green substance, which was pigment calcium and was devoid of cholesterol.

Labes [6] introduced into the gallbladders of dogs irritating, infective, alkaline and acid substances. Of these, the small or soft bodies were

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From the Department of Pathology of the University of Chicago.

1. Blachstein, A. G.: Bull. Johns Hopkins Hosp. **2**:96, 1891.
2. Welch, W. H.: Bull. Johns Hopkins Hosp. **2**:121, 1891
3. Marcantonio, A.: Riforma med., 1892, vol. 8; cited in Schmidt's Jahrb. **238**:13, 1893.
4. Gilbert, A., and Dominici, S. A.: Compt. rend. Soc. de biol. **23**:1033, 1893.
5. Mayer, Jacques: Virchows Arch. f. path. Anat. **136**:561, 1894.
6. Labes, in Naunyn, B.: A Treatise on Cholelithiasis, translated by A. E. Garrod, London, The New Sydenham Society, 1896.

expelled, while the larger or harder ones remained in the gallbladder but never became incrusted. Gallstones placed in the viscus dissolved and ultimately disappeared.

Gilbert [7] found a stone in the gallbladder of a dog previously inoculated with B. coli-communis.

Mignot [8] was unable to produce stones in the gallbladders of dogs and guinea-pigs by the introduction of foreign bodies. Injection of attenuated strains of B. coli resulted in three small biliary calculi in one guinea-pig. He also tamponed the gallbladder of a dog, in the presence of colon bacilli, for one month, after which the tampon was removed. Fourteen months later, the viscus contained from seven to eight facetted stones. These he called cholesterol stones without reporting any analysis.

Richardson [9] injected agglutinated cultures of B. typhosus into the gallbladder of a rabbit and succeeded in producing a firm, brown calculus. No analysis of the stone was reported. The same use of an ordinary bouillon culture of B. typhosus in another rabbit failed to produce a concretion.

Cushing [10] produced stones in a similar manner, except that he added another factor, intentionally traumatizing the gallbladder by firmly squeezing it between the fingers for some time after the inoculation. He also produced stones up to 3 mm. in diameter by injecting B. typhosus into the ear vein of a rabbit accompanied by trauma to the gallbladder. According to Cushing, these stones were composed chiefly of bile pigments combined with calcium. Some of them were coated with cholesterol.

Miyake,[11] working with dogs, was unable to produce stones by infection of the gallbladder with B. coli, by tying of the cystic duct or by introduction of foreign bodies into the gallbladder, although the last method resulted in incrustation of the glass pearls or particles of granite with bile pigment. The introduction of foreign bodies into the gallbladder along with infection of the organ gave this same incrustation. Ligating the cystic duct in the presence of an infection with B. coli, in a dog, resulted in the formation of two facetted stones after nine months. Foreign bodies in the gallbladder plus infection of it, with ligation of the cystic duct, led to the formation of small stones of calcium, cholesterol and pigment in two dogs. One year after infecting the gallbladder of a rabbit with B. coli and narrowing the cystic duct by

7. Gilbert, A.: Arch. gén. de méd. **2**:257, 1898.

8. Mignot, R.: Arch. gén. de méd. **2**:129, 1898; Recherches expérimentales et anatomiques sur les cholécystites, Thèse, Paris, 1896.

9. Richardson, M. W.: J. Boston Soc. M. Sc. **3**:79, 1898-1899.

10. Cushing, H.: Bull. Johns Hopkins Hosp. **10**:166, 1899.

11. Miyake, H.: Mitt. a. d. grenzgeb. d. Med. u. Chir. **6**:479, 1900.

placing a piece of gauze under it, Miyake found in the gallbladder a stone which he reported to be rich in cholesterol and containing pigment and much calcium.

Italia [12] reported the production of concretions by intravesical injection of attenuated cultures of B. typhosus and B. coli into the gallbladders of both dogs and rabbits. The calculi resembled human stones on both gross and microscopic examination, and chemically were shown to contain all the elements found in human stones.

Carmichael [13] inserted a pebble into the gallbladder of a dog and three weeks later injected B. typhosus into the organ. After a month, he found a crystalline deposit of calcium carbonate on the pebble. Glass beads left in the gallbladders of rabbits for four and one-half months were covered by hard, sterile masses composed chiefly of carbonate of lime, protein material and bile pigments. A piece of pith, however, unaccompanied by infection, produced no change. Pith infected with either B. coli or B. typhosus became surrounded by a curdy mass of carbonates and protein material. None of these foreign body coatings contained cholesterol.

Klinkert [14] repeated Cushing's experiments, injecting aviruient typhoid bacilli into the ear vein of the rabbit. In three of nine rabbits gallstones developed composed of organic substance and pigment calcium without cholesterol.

Chalatow [15] fed cholesterol to rabbits in daily doses of from 0.2 to 1.5 Gm. in from 3 to 25 cc. of sunflower seed oil, for from ten to one hundred and forty-two days. Five of the eight fed showed no evidence of formation of stones. The gallbladder of one rabbit contained some sand of crystalline cholesterol after twenty-six days. Another, after eighty-one days, contained considerably more of this sand. In a third, which lived one hundred and forty-two days, he found this same sand and a "large" crystalline concretion resembling a human cholesterol calculus, but without analysis.

Aoyama [16] tied the cystic duct in fourteen rabbits and in three guinea-pigs. He discovered cholesterol concretions in all but six animals. Eight rabbits and three guinea-pigs received four injections of 0.3 Gm. of cholesterol or cholesterol esters in 1 cc. of ether, subcutaneously every other day. The cystic duct was then ligated. Cholesterol concretions were found in all the animals. Feeding of cholesterol by stomach tube daily for from eight to ten days in four rabbits also produced cholesterol stones. The character of the stones was estab-

12. Italia, F. E.: Policlinico, 1901; cited, Zentralbl. f. Chir. **28**:693, 1901.
13. Carmichael, E. S.: J. Path. & Bact. **8**:453, 1903.
14. Klinkert, D.: Berl. klin. Wchnschr. **48**:335, 1911.
15. Chalatow, S. S.: Beitr. z. path. Anat. u. z. allg. Path. **57**:85, 1913.
16. Aoyama, T.: Deutsche Ztschr. f. Chir. **132**:234, 1914.

lished by the crystalline structure, by the solubility in chloroform with reprecipitation in the form of cholesterol crystals, and by the positive color reactions for cholesterol in a chloroform solution of the stones.

Rosenow [17] reported that dogs and rabbits surviving for a long time intravenous injection of streptococci isolated from the gallbladders of patients with cholecystitis not infrequently showed beginning formation of gallstones. He reported later [18] that of eighty animals so treated, six rabbits and three dogs showed definite formation of minute black gallstones, with cholecystitis found constantly. No further description of these stones was given.

Greig [19] found that of eighteen rabbits dying after a long course of intravenous injections of cholera vibrios, nine showed gallstones that, he said, on examination were found to be made up of cholesterol.

Emmerich and Wagner [20] exposed the gallbladders of rabbits and injected 0.5 cc. of a twenty-four hour culture of typhoid bacilli in sodium chloride solution from two to three weeks after immunizing the animals with three doses of typhoid serum. Their animals lived from one hundred to three hundred and forty-one days after operation. Cholecystitis resulted in almost every case, and calculi, measuring from pinhead size to 0.5 cm. in diameter, were found in five of sixteen rabbits. These concretions were considered to be of organic material only, since they burned without residue, showed only a slight cholesterol reaction and gave no pigment reaction.

Dewey [21] injected emulsions of cholesterol intraperitoneally and intravenously into rabbits. One animal receiving 10 cc. of a 2 per cent emulsion intraperitoneally three times a week for forty injections showed no formation of a stone, while another under the same treatment for fifty-two injections showed a few small concretions in the gallbladder. A third received the same injections daily for fifty-eight injections. The gallbladder was filled with small and larger stones. Two rabbits receiving from 5 to 10 cc. of a 1 per cent emulsion, in one case three times a week for sixteen doses and in the other case daily for thirty doses, showed no formation of stones. The combination of thirteen daily intravenous injections with ten daily intraperitoneal injections resulted in the formation of numerous small concretions. Two rabbits received a few intravenous injections followed by a long resting period and then received a few intraperitoneal injections. The gallbladder of one was negative for stones, while that of the other contained numerous

17. Rosenow, E. C.: J. A. M. A. **63**:1835, 1914.
18. Rosenow, E. C.: J. Infect. Dis. **19**:527, 1916.
19. Greig, E. D. W.: Indian J. M. Research **3**:259 and 397, 1915-1916.
20. Emmerich, and Wagner, G.: Centralbl. f. allg. Path. u. path. Anat. **27**:433, 1916.
21. Dewey, K.: Arch. Int. Med. **17**:757, 1916.

small concretions. The gallstones were irregular, brittle, not facetted and black. Sections of them examined microscopically showed them to be made up of a framework of disintegrated cells held together by pigment and calcareous substances, forming parallel trabeculae. Chemical examination was not reported.

Venema [22] made typhoid carriers of rabbits by injecting into the gallbladder one-half loop of a twenty-four hour typhoid agar culture in 0.5 cc. of physiologic solution of sodium chloride. In one animal, he found a soft, bright yellow concretion from 3 to 4 mm. in diameter, which was not analyzed.

Sotti and Torri [23] reported that in 1913 they found sterile concretions of definite morphology in the gallbladders of rabbits after splenectomy and ligation of the ductus choledochus. The chemical structure of the stones was not reported.

Iwanaga [24] repeated Aoyama's work. Ligation of the cystic duct, with or without feeding of cholesterol, caused the formation of an amorphous mass in the gallbladder not similar to a gallstone. Subcutaneous injections of cholesterol had no influence on the cholesterol content of the bile and did not cause the formation of these amorphous structures.

Meyer and his co-workers,[25] by intravenous and cystic injection of typhoid bacilli, made rabbits chronic carriers. In the gallbladders of the animals that survived for from one hundred to eight hundred and sixteen days were found, invariably, yellowish-green biliary concretions or blackish calculi, consisting of lime salts with traces of bile pigment and organic material, but with no cholesterol. No calculi were found in the gallbladders of the rabbits living less than thirty days, but they were found in all animals surviving the infection one hundred days or longer.

Badile [26] infected the gallbladders of dogs with B. coli and B. typhosus after narrowing the ductus choledochus in each with a ligature. Cholecystitis resulted, but there was no evidence of formation of stones. Narrowing the duct and placing gauze or silk thread in the gallbladder caused only slight precipitation on the foreign body. When a fine cholesterol emulsion was introduced into the dogs' gallbladders after the duct in each had been narrowed, small cholesterol

22. Venema, T. A.: Berl. klin. Wchnschr. **54**:815, 1917.

23. Sotti, G., and Torri, O.: Pathologica **12**:369, 390 and 423, 1920.

24. Iwanaga, H., cited in Centralbl. f. allg. Path. u. path. Anat. **33**:191, 1922.

25. Meyer, K. F.; Neilson, N. M., and Feuisier, M. L.: J. Infect. Dis. **28**:456 and 510, 1921.

26. Badile, L.: Pathologica **15**:307, 1923.

concretions formed. These stones were fragile and gave positive reactions for bile pigment and cholesterol. Microscopically, they showed an amorphous structure inclosing cholesterol granules.

Rous et al.[27] discovered incidentally that small calcium carbonate and calcium bilirubinate stones were formed along the glass and rubber tubings after intubating the gallbladders of dogs for the collection of bile under sterile conditions.

Agrifoglio [28] loosely ligated the common bile duct in dogs, and then injected colon and typhoid bacilli intravenously or into the gallbladder. Concretions formed only in those animals in which attenuated typhoid bacilli had been injected directly into the gallbladder.

Engel and Cserna [29] repeated some of Dewey's experiments. They injected a 2 per cent emulsion of cholesterol daily into the peritoneal cavities of seven rabbits for from four to ten months but were unable to produce gallstones in any case.

Fujimaki [30] observed that in rats fed for a long time on a diet deficient in vitamin A there developed, in sequence, bladder, renal and bile duct calculi. The biliary calculi consisted mainly of cholesterol and pigment. Neither lack of vitamin B nor restriction of the protein seemed to be concerned in such formation of stones.

Stern [31] found no cholesterol coagulation in the gallbladders of rabbits after ten daily intravenous injections of cholesterol.

Hansen [32] fed eight rabbits cholesterol in oil in doses of from 0.5 to 1 Gm. daily for from five to seventy-seven days. In four, cholesterol crystals of microscopic size developed in the gallbladder. One, fed 0.5 Gm. for twelve days, showed three pinpoint-sized pearls of cholesterol. A rabbit that received 10 cc. of a 1 per cent emulsion of cholesterol intraperitoneally once daily for sixty days also showed the cholesterol crystals. Another rabbit that received this same solution subcutaneously, intraperitoneally and intravenously once daily for sixty-six days showed clumps of cholesterol in the gallbladder. The injection of this solution intraperitoneally daily for fifty-six days into a rabbit, which then received cholesterol by stomach tube for eighteen days, resulted in the formation of many pigment kernels and cholesterol crystals in the gallbladder. By narrowing the cystic duct of the gallbladder with a ligature in otherwise normal rabbits, Hansen produced

27. Rous, P.; McMaster, P. D., and Drury, D. R.: J. Exper. Med. **39**:77, 1924.
28. Agrifoglio, M.: Clin. med. ital. **55**:89, 1924.
29. Engel, K., and Cserna, S.: Wien. klin. Wchnschr. **38**:123, 1925.
30. Fujimaki, Y.: Formation of Urinary and Bile-Duct Calculi in Animals Fed on Experimental Rations, in Saiki, T.: Progress of Science of Nutrition in Japan, League of Nations Health Organization, C. H. 523, Geneva, 1926, p. 369.
31. Stern, R.: Arch. f. exper. Path. u. Pharmakol. **112**:129, 1926; **131**:221, 1928.
32. Hansen, S.: Acta chir. Scandinav. **62**:483, 1927.

pigment stones without cholesterol content. This same procedure in hypocholesteremic rabbits, however, resulted in almost constant production of cholesterol crystal concretions.

Whitaker [33] reported soft masses in the gallbladders of four of sixteen cats after cutting and dilating the sphincter of the common bile duct.

Copher and Illingworth [34] repeated Whitaker's experiment on eighteen cats, but were unable to confirm his results. They also combined this procedure with the introduction of B. coli, staphylococci and streptococci in the gallbladders of cats, but found no cystitis or lithiasis even after several weeks. The same infection in dogs together with ligation of the common duct below the middle hepatic duct gave the same result. Cutting the sphincter in cats together with the introduction of many kinds of foreign bodies into the gallbladder, and in some cases with infection of the viscus, gave negative results. Nor could they produce stones by cauterization of either the mucosa or the serosa of the gallbladder with phenol after cutting the sphincter in cats.

Wilkie,[35] as did Rosenow, injected streptococci isolated from human gallbladders into the lumen of the gallbladder, into the wall of the gallbladder and intravenously in rabbits. The intravesical method gave negative results. The intramural method after three months produced an inflamed gallbladder, which contained pinhead-sized stones composed of large amounts of cholesterol but no calcium. The intravenous method was fruitless until, by repeated injections, chronic cholecystitis was produced, occasionally accompanied by the formation of cholesterol stones without trace of calcium. Injecting the streptococci intramurally with the cystic duct ligated produced stones in some cases. These stones contained a large amount of calcium as well as cholesterol. Repeated intravenous injection of the organisms with the cystic duct ligated resulted in the formation of stones composed mostly of calcium with but relatively little cholesterol.

Whitaker [36] stated that chemical examination of the masses that he produced in 1927 revealed them to be largely blood clots. He then reported masses resembling stones found in seven of nine cats, which he had produced by inducing stasis and hyperconcentration of bile through fasting and dehydration for from five to fifteen days while the animals were kept sleeping peacefully under barbital anesthesia.

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33. Whitaker, L. R.: J. A. M. A. **88**:1542, 1927.

34. Copher, G. H., and Illingworth, C. F. W.: Surg., Gynec. & Obst. **46**:658, 1928.

35. Wilkie, A. L.: Brit. J. Surg. **15**:450, 1928.

36. Whitaker, L. R.: Surg., Gynec. & Obst. **48**:396, 1929.

The stones consisted of numerous particles ranging in diameter from that of a grain of dust up to 1 to 2 mm. and varying in consistency from semisolid to solid. No chemical analysis was reported.

Illingworth,[37] studying the "strawberry" gallbladder, reported the production of a large, semisolid concretion in the gallbladder of a single rabbit by feeding 0.2 Gm. of cholesterol daily for thirteen weeks and making an intramural injection of streptococci one week after the beginning of the feeding. No analysis or further description of the stone was reported.

Usuki [38] fed young rabbits a diet deficient in the fat-soluble vitamins for periods of from thirty-five to one hundred and seven days. Of the forty-three animals used, four developed numerous minute (millet seed) concretions.

Westphal and Gleichmann [39] narrowed the cystic duct in dogs for varying periods of time and combined this stasis with feeding of cholesterol and also with injections of animal charcoal and sodium chloride into the gallbladder. They succeeded in producing bilirubin concretions, usually of pinhead size, but in one case measuring up to 1 cm. in diameter. Microscopic examination of the bile from some of the animals fed cholesterol showed globules, presumably of cholesterol, radiating about the surface of minute pigment concretions. No cholesterol stones were found.

In summary, we find that, in the main, five methods have been used to produce calculi: introduction of foreign bodies into the gallbladder, production of stasis in the gallbladder, infection of the organ, induction of hypercholesteremia and production of a deficiency of vitamins. The use of foreign bodies even when combined with infection has resulted only in a coating of the bodies with a layer of pigment, and that only occasionally. Stasis in the gallbladder alone has given no results, except in one instance (Hansen) in which a pigment stone, without cholesterol content, was formed. Infection, alone and with stasis, has resulted in the formation of stones on many occasions. Often these stones were described as cholesterol stones, but in those instances in which analyses were made, the concretions were found to be either pigment stones, with or without calcium carbonate, or organic material consisting chiefly of tissue débris without appreciable cholesterol content. Cholesterol stones have been reported in a few instances in hypercholesteremic animals, and the character of the stones has been substantiated by analysis. Yet the animals in which positive results

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37. Illingworth, C. F. W.: Brit. J. Surg. **17**:203, 1929.

38. Usuki, K.: Jap. J. Gastroenterol. **1**:18, 1929.

39. Westphal, K., and Gleichmann, F.: Ztschr. f. klin. Med. **115**:329, 1931.

were shown numbered but a few of those used in each series, and other investigators have failed to confirm the results. Hypercholesteremia combined with stasis in the gallbladder has given no better success. A few workers have reported finding minute cholesterol stones in vitamin-deficient animals. Too little information is available at this time to come to any conclusion concerning the application of these findings. Strangely, the combination of infection and hypercholes-

Data of Experiments

Rabbit	Length of Time Given 2 Injections of Cholesterol Weekly	Length of Time Survived Injections of Typhoid Bacilli	Cholecystitis	Gallbladder Content
1	6 wks.	(No injection)	0	Normal
2	7 wks.	(No injection)	0	Normal
3	2 mos.	(No injection)	0	Normal
4	2 mos.	(No injection)	0	Numerous hard pigment stones up to 1 mm. in diameter
5	2 mos.	(No injection)	0	Cholesterol crystals in the bile
6	4 mos.	(No injection)	0	Many minute pigment granules
7	5 mos.	(No injection)	0	Normal
8	(No cholesterol given)	5 mos.	Definite	Plug of cellular débris
9	(No cholesterol given)	16 mos.	Very definite	Lumen obliterated
10	3 mos.	12 mos.	0	Normal
11	5 mos.	12 mos.	0	Normal
12	5 mos.	5 mos.	0	Clear bile containing numerous minute, hard pigment granules
13	3 mos.	1 mo.	Definite	Cheesy, organic débris
14	4 mos.	3 mos.	Very definite	Organic débris and many hard pigment granules (2 x 1 mm.)
15	6 mos.	3 mos.	Slight	Cellular débris and microscopic hard pigment granules
16	5 mos.	7 mos.	Slight	Soft pigment clumps in bile
17	9 mos.	10 mos.	Slight	Many soft pigment clumps up to 1 mm. in diameter
18	2 mos.	2 mos.	Slight	Organic débris, small pigment granules, microscopic cholesterol crystals
19	6 mos.	11 mos.	Slight	Clumps of soft organic débris and cholesterol crystals in bile
20	5 mos.	3 mos.	Definite	Cellular débris and very numerous cholesterol crystals
21	6 mos.	10 mos.	Very definite	Heavy precipitate of cholesterol with 8 pigment clumps up to 3.5 mm. in diameter

teremia has not been extensively tried. Illingworth found his concretion incidentally. The experimental work that I shall now describe concerns an attempt to produce cholesterol gallstones in rabbits by a combination of these two factors, continued high blood cholesterol plus infection of the gallbladder.

METHOD

A 1 per cent watery emulsion of cholesterol was made according to the method described by Dewey.[21] Healthy rabbits each received 10 cc. of this emulsion intraperitoneally twice a week for varying periods up to nine months. The blood cholesterol changes were followed, and after the animals had become hypercholesteremic, the abdomen of each was opened, 1 cc. of bile was aspirated from the

gallbladder, and about 1 cc. of a suspension of a twenty-four hour growth of typhoid bacilli was injected into the viscus. To prevent leakage into the peritoneal cavity, the needle was inserted into a tip of the liver, through the thin mesentery of the gallbladder, and thence through the wall of the gallbladder. The bile was aspirated, and the organisms injected through the same needle without removing it between the operations, so that only a single puncture was made. The abdomen was closed, and after two weeks' rest, the injections of cholesterol were continued. The typhoid infection was produced from two to ten weeks after the injections of cholesterol were started, and these injections were continued for from five to thirty-two weeks after the infection. A few of the animals were killed. Some of them died from peritonitis resulting from the intraperitoneal injections. Those surviving the injections were left undisturbed to die of natural causes. These died from one to eight months after cessation of the injections.

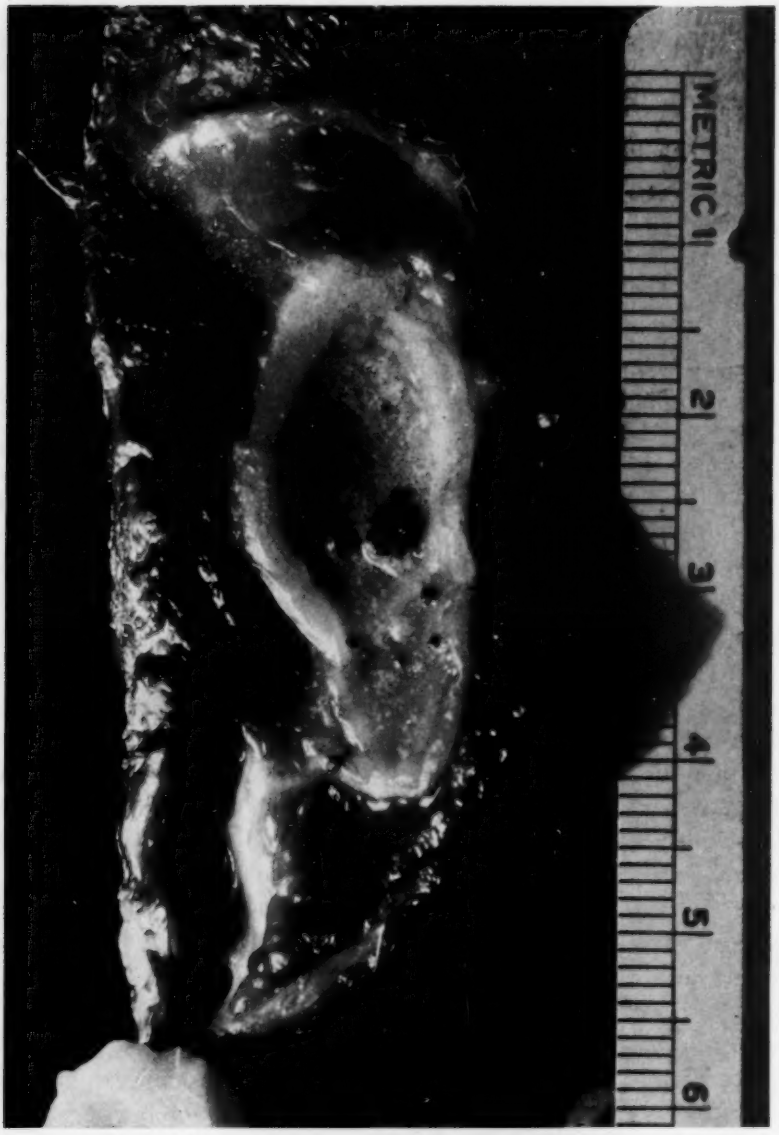
OBSERVATIONS

Of the seven rabbits receiving injections of cholesterol only, four showed no biliary changes. Only one showed any cholesterol change in the gallbladder, and that was in the form of fine cholesterol crystals in the bile. Strangely, the bile of two rabbits contained black concretions, in one case of pinhead size, in the other measuring up to 1 mm. in diameter. These granules were irregular in outline and very hard. They contained no cholesterol, but were composed of calcium bilirubinate. The wall of the gallbladder was normal in all seven rabbits.

Both of the rabbits (8 and 9) receiving only the intravesical injection of typhoid bacilli showed marked chronic cholecystitis. The wall of the gallbladder was white, opaque and very thick. In the rabbit living five months after infection, the lumen of the viscus contained a plug of white, cellular débris and no bile. The gallbladder of the rabbit killed after sixteen months had a wall measuring 1 mm. in thickness, and the lumen was almost entirely obliterated.

Of the twelve rabbits receiving both the cholesterol and the typhoid injections, three showed a normal wall of the gallbladder with no evidence of infection. The bile was also normal in two of these, but in the third it showed pigment granules similar to those seen in the first group of animals. The other ten showed cholecystitis of varying degrees of intensity. In five there was slight thickening of the wall with a moderate degree of lymphocytic infiltration into the wall, as described in typhoid carriers (Mallory [40]). In two, this process was more severe, and there was some hypertrophy with fibrosis of the wall. The other two showed a very thick wall, composed largely of dense fibrous tissue. All of these ten showed changes in the bile. The bile in each case contained the organic débris seen in the rabbits receiving

40. Mallory, T. B., and Lawson, G. M.: Am. J. Path. **7**:71, 1931.



The gallbladder of rabbit 21. The rabbit received biweekly intraperitoneal injections of cholesterol for two months, followed by an intravesical injection of B. typhosus and a continuance of the injections of cholesterol for another four months. The animal was killed seven months later. Note the tremendously thickened wall of the gallbladder, the ten pigment concretions in the bile (one lies in the cystic duct, but does not occlude it) and the innumerable flecks of cholesterol present both in the bile and in the mucosa of the gallbladder.

only the typhoid bacilli. The gallbladders of two of them also contained the hard pigment granules seen in the first group of rabbits receiving only the cholesterol. Six of the rabbits, however, showed further changes in the bile: In four, soft, brown clumps were found that did not resemble the small, hard, black granules of pigment, and at first these were thought to be masses of cholesterol. On analysis, however, the masses were shown to contain only traces of cholesterol and consisted largely of calcium bilirubinate. In two of these rabbits there were also found in the bile large numbers of cholesterol crystals. Two other rabbits showed these crystals, but not the clumps of pigment. Rabbit 21 showed the condition illustrated in the accompanying photograph. The wall of the gallbladder was markedly thickened; the bile was filled with large flakes of yellowish cholesterol and contained ten soft concretions, the largest measuring irregularly 3.5 mm. in diameter. One of the smaller stones can be seen in the beginning of the cystic duct, where it was found lying loosely without occluding the duct. The bile was filled with precipitated cholesterol; yet an alcohol-ether extraction of the concretions showed only a trace of cholesterol on precipitation with digitonin.

COMMENT

Why two of seven hypercholesteremic rabbits should show pigment concretions in their gallbladders is unexplained. Hansen [32] described similar findings. The literature contains no reference to spontaneous gallstones in rabbits. Only one of the seven showed cholesterol crystals in the bile. Of the ten hypercholesteremic rabbits with infected gallbladders, four showed cholesterol crystals in the bile, and two of these and two others showed changes in bile pigment not seen in the rabbits with noninfected gallbladders.

Although the method used failed to produce the desired result, cholesterol gallstones, yet it did result in precipitating out of the bile the elements making up gallstones. Many authors believe that cholesterol stones form by accumulation of precipitated cholesterol on bile pigment nuclei. Others feel that organic débris is the nidus. Four of the infected rabbits showed precipitation of cholesterol in the bile, six of them showed pigment nuclei, and all of them showed cellular débris in the bile. Pigment stones had formed, but no great quantity of cholesterol was adherent to the surfaces in the two cases in which both elements were present; nor had the cholesterol coated the cellular débris in the four cases in which the crystals and débris existed together. Whether some additional factor is necessary to lead to accumulation of the cholesterol on the nidus, or whether it is merely a question of greater time required for the growth of the stone, demands further investigation.

SUMMARY

A combination of hypercholesteremia, induced by intraperitoneal injections of a watery emulsion of cholesterol, and infection of the gallbladder, produced by direct cystic injection of B. typhosus, failed to lead to the formation of cholesterol gallstones in rabbits. Pigment calculi were formed in many of the gallbladders, and in some of the rabbits cholesterol crystals were found in the bile. In no instance, however, had any appreciable quantity of the cholesterol been incorporated in or incrusted on the pigment stones.

The numerous methods used in attempts to produce gallstones experimentally are given in a review of the literature. Foreign bodies in the gallbladder have frequently become coated with pigment. Stasis alone has been unsuccessful, but when combined with infection has, on occasion, led to the formation of pigment stones often combined with carbonates. Cholesterol stones have been found in hypercholesteremic animals in a few instances, but these results have failed of confirmation. Recently, minute cholesterol stones have been reported in a few vitamin-deficient animals. Various combinations of the methods named have given no better results. No method has been found that will produce gallstones, especially of the cholesterol type, with any degree of certainty.

General Review

THE PATHOLOGIC PHYSIOLOGY OF THE PARATHYROID GLANDS

KURT SEMSROTH, M.D.
AND
HARRY B. McCLUGAGE, PH.D.
PITTSBURGH

Until recently knowledge of the rôle of the parathyroid glands in health and disease was based almost exclusively on animal experimentation. Such experimentation was stimulated primarily by the experiences of surgeons in cases of "total" thyroidectomy, such as the observance of the frequent occurrence of symptoms of tetany following this operation. In view of the proximity and the close histologic similarity of the parathyroid gland to the thyroid gland, no independent significance was attached to them until Gley [1] made his fundamental experiments. He was the first to show that in rabbits tetany ensued when the parathyroid glands were removed with the thyroid gland, but that tetany did not ensue when the parathyroid glands were left behind. Gley and a number of other observers, finding an enlargement of the parathyroid glands that had been left behind in a thyroidectomy, concluded that these enlarged glands compensated for the function of the removed thyroid gland. The conception of a compensatory rôle of the parathyroid glands was definitely refuted by the work of Vassale and Generali.[2] They found that removal of all parathyroid glands resulted in fatal tetany even when the entire thyroid gland was left behind. When, on the other hand, these investigators removed the entire thyroid gland, but spared one or several of the parathyroid glands, tetany did not develop in the animals. These experiments, corroborated by numerous additional observers, furnished proof of a causal relationship between removal of the parathyroid glands and tetany, and led to the establishment of the symptom complex of "tetania parathyreopriva."

From the Western Pennsylvania Hospital Institute of Pathology, Ralph R. Mellon, Director.

1. Gley: Compt. rend. Soc. de biol., 1891, pp. 557, 567, 583 and 843.

2. Vassale and Generali: Riv. di pat. nerv. **1**:249, 1896; Arch. ital. di biol. **25**:459, 1896; **26**:61, 1896.

In dogs, after parathyroidectomy, some of the earliest symptoms of an attack of tetany are loss of appetite and increasing restlessness. Later there appear fine fibrillary contractions of the temporal muscles, then of other muscles of the head and jaw. Recovery from such an attack is often followed by other and more severe attacks at progressively shorter intervals. Death is commonly produced by asphyxia resulting from spastic contraction of the larynx and the muscles of respiration (Dragstedt [3]).

Once the importance of parathyroid function had been demonstrated, the efforts of investigators centered for many years on the problem of the sequelae of parathyroidectomy. It soon became doubtful whether removal of the parathyroid glands was the sole and direct cause of tetany. When animals, subsequent to a partial parathyroidectomy, had recovered from the postoperative tetany, they were found to be in a state of latent tetany. A number of factors would, in such animals, elicit tetany. Among these factors, pregnancy was quite well established. Trauma, psychic trauma, exhaustion and infection were also found to play a rôle. Nutritional factors also are evidently of considerable importance. A diet rich in meat has, in the experience of several investigators, tended to aggravate postoperative tetany, while a diet rich in milk has, in some experiments, served to arrest the fatal consequences of parathyroidectomy. It is apparent from such observations that parathyroidectomy as such does not cause tetany, but increases the nervous irritability to such an extent that normally harmless factors elicit tetany in these animals.

Following a nonfatal parathyroidectomy, chronic pathologic consequences ensue. Cachexia and psychic disturbances have been observed, and symptoms referable to a disturbance of the mineral metabolism have been the object of numerous investigations. The appearance of cataract and the shedding of the hair have been noted.

RELATION TO CALCIUM AND PROTEIN METABOLISM

Of outstanding importance have been observations on changes in the teeth following parathyroidectomy. Erdheim [4] first directed attention to chronic sequelae of parathyroidectomy in rats when he found that in these animals the newly formed dentin of the gnawing teeth calcifies either too late and in a faulty way or not at all. In contrast to the physiologically regenerating gnawing-teeth, the other teeth, which were fully developed at the time of the parathyroidectomy, remained unaf-

3. Dragstedt: Physiol. Rev. **7**:499, 1927.

4. Erdheim: Wien. klin. Wchnschr. **19**:716 and 817, 1906.

fected. Erdheim's observations were amplified and fully corroborated by Toyofuku.[5] It became apparent that the disturbance of calcium metabolism subsequent to removal of the parathyroid glands is not restricted to the dentin of growing teeth. Erdheim [6] was able to show that in these animals, young or adult, fractures of the bones heal by the slow formation of a callus that is remarkably poor in calcium salts. He compared these findings with those in human rickets and osteomalacia. Chemical analyses of the bones of such animals were carried out by Ogawa,[7] who found a decrease in calcium of the bones, particularly marked in cases in which tetany developed. A decrease in calcium subsequent to parathyroidectomy was further observed in the brain by MacCallum and Voegtlin [8] and in the blood serum by MacCallum, Hastings and Murray,[9] and by many other investigators. On the other hand, an increase in the excretion of calcium through the urine of these animals could not be corroborated by Cooke.[11] Although a number of investigators were unable to find a decrease in calcium in the serum and central nervous system of the animals operated on, these negative results do not refute the importance of the calcium metabolism among the sequelae of parathyroidectomy.

From the researches of Loeb [12] it is known that muscular irritability depends on the quantitative relation between calcium ions on the one hand and potassium and magnesium on the other. A relative decrease in the number of calcium ions leads to muscular spasms. When we consider that, according to Rona and Takahashi,[13] only one fifth of the total calcium of the blood is present as calcium ions, it becomes clear that even in the absence of a decrease in the total serum calcium the number of calcium ions may be decreased. The significance of the calcium ion concentration of the blood was demonstrated by the experiments of MacCallum, Lambert and Vogel.[14] They removed the calcium ions from blood by dialysis. This blood then induced muscular spasms; on addition of calcium, it lost its spastic effect. Using the frog's heart as an indicator for the calcium ion concentration, Trendelenburg and

5. Toyofuku: Frankfurt. Ztschr. f. Path. **7**:249, 1911.

6. Erdheim: Frankfurt. Ztschr. f. Path. **7**:175, 1911.

7. Ogawa: Arch. f. exper. Path. u. Pharmakol. **109**:83, 1925.

8. MacCallum and Voegtlin: J. Exper. Med. **11**:118, 1909; Bull. Johns Hopkins Hosp. **19**:91, 1908.

9. Hastings and Murray: J. Biol. Chem. **16**:233, 1921.

10. Footnote deleted by the author.

11. Cooke: J. Exper. Med. **21**:45, 1910.

12. Loeb: Am. J. Physiol. **3**:327, 1900.

13. Rona and Takahashi: Biochem. Ztschr. **31**:336, 1911.

14. MacCallum; Lambert, and Vogel: J. Exper. Med. **20**:149, 1914.

Goebel [15] found a definite decrease in the number of the calcium ions in the serum of cats subsequent to parathyroidectomy.

The inference, then, that the removal of the parathyroid glands leads to a disturbance of the calcium metabolism appears justified. Whether this metabolic disturbance is directly or indirectly referable to the parathyroidectomy is still somewhat a matter of dispute. A decrease in the H-ion concentration in tetany was pointed out by Wilson, Stearns and Janney [16] and others—an observation that may lead one to interpret the decreased calcium concentration of the blood after parathyroidectomy as due to "alkalosis" of the blood. A number of observers stress the importance of increased phosphorus content of the serum subsequent to removal of the parathyroid glands (Greenwald [17] and others), since this increase in phosphorus would also in itself lead to a decrease in the calcium ion concentration.

In the opinion of some workers, parathyroidectomy leads primarily to a disturbance of intermediate protein metabolism. The latter, in turn, through the resulting alkalosis, induces a decrease in the calcium ion concentration. This contention appears to be based principally on the following facts: Koch [18] found that following parathyroidectomy certain protein split products, the guanidines, appear in increased quantity in the urine. His observations were corroborated by those of Paton and Findlay [19] and others. As further supporting this view, the guanidine contents of the muscles were found diminished by Henderson.[20] In addition, Paton,[21] experimenting with cats, found that the symptoms of guanidine poisoning were highly analogous to those of "tetania parathyreopriva." In particular, he pointed out that the animals showed the same type of electric hyperirritability that is characteristic of tetany after removal of the parathyroid glands. The work of Paton and Findlay,[19] and that of Herxheimer,[22] on guanidine poisoning after parathyroidectomy led these authors to conclude that subsequent to this operation the susceptibility to the effects of guanidine is doubled.

On the basis of the observations on guanidine in animals after removal of the parathyroid glands, the resulting tetany has been

15. Trendelenburg and Goebel: Arch. f. exper. Path. u. Pharmakol. **89**:171, 1921.

16. Wilson; Stearns, and Janney: J. Biol. Chem. **23**:89, 1915.

17. Greenwald: Am. J. Physiol. **28**:103, 1911; Biochem. Ztschr. **54**:159, 1913.

18. Koch: J. Biol. Chem. **12**:313, 1912.

19. Paton and Findlay: Quart. J. Exper. Physiol. **10**:315, 1916.

20. Henderson: J. Gen. Physiol. **52**:1, 1918.

21. Footnote deleted by the author.

22. Herxheimer, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8, p. 548.

interpreted as guanidine poisoning (Biedl [23]). It was thought that parathyroid insufficiency, through an increased effect of guanidine, led to alkalosis and that the latter, bringing about a decrease in calcium ion concentration, then led to hyperirritability of the nervous system (Herxheimer [22]). The findings of Berkeley and Beebe [24] point in a similar direction. These investigators observed that after parathyroidectomy the administration of calcium was of no therapeutic avail, especially when the animals were put on a meat diet.

Analogies appear to exist between the sequelae of parathyroidectomy on the one hand and symptoms associated with spontaneous hemorrhages into the parathyroid glands of children on the other hand. The considerable frequency of hemorrhage into the marginal parts of the parathyroid glands of children under 5 years of age was pointed out by Yanase,[25] who found its occurrence in thirty-three of eighty-nine cases. He had occasion to examine thirteen children who during life had shown a normal electric irritability, but in none of these did he observe parathyroid hemorrhage. On examination of seventeen children under 1 year of age, who had shown electric hyperirritability, parathyroid hemorrhage was seen in every case. With thirteen children over 1 year, who also had shown electric hyperirritability, parathyroid hemorrhage was found only in three cases. From the investigations of Yanase and others, we infer that a relationship may exist between electric hyperirritability and disturbances of parathyroid growth resulting from hemorrhage rather than the parathyroid hemorrhage as such. However, workers on this subject do not agree that the incidence of parathyroid hemorrhage with electric hyperirritability is actually higher than without such hyperirritability as claimed by Yanase.

THE SPECIFIC HORMONE OF THE PARATHYROID GLANDS

Knowledge as to the physiology of the parathyroid glands has been gained primarily by the study of the sequelae of parathyroidectomy, as briefly summarized in the preceding section. This information led to therapeutic attempts. One tried to combat parathyroid insufficiency through supplying artificially the missing internal secretion of the gland. While it had not been possible to extract from the parathyroid gland a regularly effective endocrine principle prior to the recent work of Hanson [26] and Collip,[27] early workers made successful use of transplantation of the parathyroid gland. Pool [28] was the first to transplant

23. Biedl: Innere Sekretion, Vienna, 1922.
24. Berkeley and Beebe: J. M. Research **20**:149, 1909.
25. Yanase: Jahrb. f. Kinderh. **67**:45, 1908.
26. Hanson: Mil. Surgeon **54**:218, 1924.
27. Collip: J. Biol. Chem. **63**:461, 1925.
28. Pool: Ann. Surg. **46**:507, 1907.

a human parathyroid gland in a case of tetany after strumectomy. The success of such transplantation was found to be transitory by numerous workers. Eiselsberg [29] in 1922 gave the number of successful transplantations in man to that time as twenty.

In view of the transitory results attained, most investigators arrived at the conclusion that the transplanted parathyroid gland would, after a certain time, cease to function, and that thereafter recurrences were bound to occur unless the other parathyroid glands regained their function. This inference is supported by the results of animal experimentation on the subject. Observers have reached the consensus that heterotransplantation is less frequently successful than autotransplantation. Some workers even found successful transplantation between individuals of the same species impossible and were able to perform only autotransplantations (Halsted [30]).

The latter experimental procedure furnished ample proof of the function of a transplanted parathyroid gland. When one transplanted part of the parathyroid glands and allowed for sufficient time for the transplants to regain a blood supply, one could then remove all the parathyroid glands that had been left in their normal position, without danger of tetany. When one subsequently removed the transplants, tetany regularly ensued. The influence of transplanted parathyroid glands on the calcium metabolism of teeth was demonstrated by Erdheim,[31] who performed autotransplantations in rats. He found that in the dentin of the gnawing teeth of these animals, a calcium-free zone appeared that corresponded to the time of temporary parathyroid insufficiency subsequent to the operation.

Attempts to combat parathyroid insufficiency by the administration of the parathyroid substance itself or extracts from it have for a considerable time met with partial success. Such extracts as the "parathyroidin" of Vassale were tried in experiments on animals and were found by some to have a beneficial effect on the tetany parathyreopriva when given intravenously in large quantities. Others, however, were unable to corroborate such a therapeutic effect. The extract of Beebe—a nucleoproteid—was found by MacCallum to suppress tetany in animals for some time. Pool [28] saw good results from this extract in human tetany after strumectomy. Biedl [23] in 1922 stated that he had found but two effective parathyroid extracts.

The work of Hanson [26] and Collip [27] led to the preparation of an active parathyroid extract. Injections of this "parathormone" abolish tetany in parathyroidectomized dogs. Application of parathormone leads

29. Eiselsberg: Wien. klin. Wchnschr. **35**:1, 1922.
30. Halsted: J. Exper. Med. **11**:175, 1909.
31. Erdheim: Frankfurt. Ztschr. f. Path. **7**:295, 1911.

to a rise in the calcium level of the serum. An effect of parathormone on the phosphorus metabolism of animals possibly precedes that on the calcium metabolism. Injection of parathormone leads to an abrupt rise in the urinary excretion of phosphorus without affecting the fecal excretion. At the same time the level of inorganic serum phosphorus is lowered. Collip [27] found that when the serum calcium has attained a certain level, further injections of parathormone bring about an abrupt rise in the serum phosphorus. Greenwald and Gross [32] observed that in normal dogs the rise in serum calcium resulting from injection of parathormone was followed by increased excretion of calcium.

Increased excretion of calcium was also stressed by Hunter and Aub.[33] These observers put patients suffering from lead poisoning on a diet poor in calcium. In these patients a negative calcium balance developed. When parathormone was then injected, an increase of the negative calcium balance ensued. Hunter and Aub concluded that parathormone administered during deficient intake of calcium causes increased excretion of calcium salts from the bones. On the contrary, Ogawa [7] reported an increase in calcium salts of the bones on feeding parathyroidectomized animals with parathyroid substance. The effect of prolonged application of parathyroid extract in animals, particularly in regard to calcium storage, has been studied by a number of investigators in the hope of gaining information on hyperparathyroidism in man. *A priori* the results of animal experimentation must be dependent on the calcium content of the diet as well as on the amount of calcium absorption from the intestinal tract. Indeed, the latter point has already been indicated in the conclusions of Hunter and Aub.[33] The significance of calcium absorption is quite apparent in the results of Morgan and Garrison,[34] who gave dogs cod liver oil or viosterol. On injection of parathormone, the animals presented a rise in serum calcium definitely higher than that in dogs which were not given cod liver oil or viosterol.

Therefore in the study of the effects of injections of parathormone it may be advisable to refer to the results as sequelae of a disturbed correlation between calcium intake and parathyroid function, rather than of a hyperparathyroidism as such. That fatal sequelae opposed to those resulting from parathyroidectomy may follow overdosage of parathormone has been shown by Collip.[27] When this investigator, by injections of parathormone, raised the serum calcium of dogs to 21 mg. per hundred cubic centimeters they presented dulness within twenty-four hours, drowsiness, atonia and failing circulation, and frequently died

32. Greenwald and Gross: J. Biol. Chem. **66**:185, 1925.
33. Hunter and Aub: Quart. J. Med. **20**:123, 1926-1927.
34. Morgan and Garrison: J. Biol. Chem. **85**:687, 1930.

within forty-eight hours after the first dose. Bauer, Aub and Albright [35] injected increasing doses of parathormone into rabbits and cats for ninety-one days, raising the serum calcium to 15 mg. per hundred cubic centimeters. On gross examination, the spongiosa of the long bones of these animals showed decreased density. It appears noteworthy that these authors also were able to induce decreased density of the spongiosa through a low calcium diet alone, and increased density through a high calcium diet.

Hueper,[36] after prolonged overdosage of parathormone in dogs, saw metastatic calcification in the kidneys, lungs, myocardium and gastrointestinal tract. Jaffé, Bodansky and Blair [37] injected parathormone into dogs and guinea-pigs, into the former for as long as six months. They were able to produce, in this manner, the typical picture of a generalized "ostitis fibrosa cystica." This condition is characterized by general osteoporosis, lacunar resorption of bone, apposition of new bone, fibrosis of the marrow and formation of giant cell "tumors" of bones, probably largely composed of osteoclasts and cysts. The disturbance of the calcium storage of the bones in these experimental animals of Jaffé does not appear to differ fundamentally from that obtained through a diet poor in calcium; in both cases, the investigators induced generalized osteoporosis. The other features of osteitis fibrosa cystica, however, could not be induced by a diet low in calcium. The latter did enhance the effect of the injections of parathormone.

The experiments of Jaffé, Bodansky and Blair have thrown light on the question of the pathogenesis of osteitis fibrosa cystica. Given a certain intake of calcium, parathyroid hormone present in the blood to excess leads to removal of calcium from the bones and the sequelae characteristic of generalized osteitis fibrosa. Discontinuance of the injections of parathormone led, with Jaffé and others, to a reversal of the process, i. e., deposition of calcium in the bones, drop in serum calcium, increase in serum phosphorus.

Several investigators have paid considerable attention to the fact that in cases of general osteitis fibrosa, as well as after injections of parathormone (Jaffé), the blood plasma shows an increase in phosphatase (Hunter,[38] Bodansky and Jaffé [39]). Phosphatase, according to Kay,[40] is an enzyme present in bone extracts that hydrolizes soluble calcium salts of phosphoric esters to give insoluble calcium phosphate.

35. Bauer; Aub, and Albright: J. Exper. Med. **49**:145, 1929.

36. Hueper: Arch. Path. **3**:14, 1927.

37. Jaffé and Bodansky: J. Exper. Med. **52**:669, 1930. Blair: Arch. Path. **11**:207, 1931.

38. Hunter: Quart. J. Med. **95**:383, 1931.

39. Bodansky and Jaffé: J. Biol. Chem. **92**:16, 1931.

40. Kay: Brit. J. Exper. Path. **10**:253, 1929; J. Biol. Chem. **89**:267, 1930.

It is present in growing bone in the localities in which deposition of calcium phosphates is most rapidly proceeding. It is absent in cartilage. Robison [41] stressed the rôle of phosphatase in the formation, maintenance and repair of bone. Whether the increase of plasma phosphatase subsequent to injections of parathormone precedes the removal of calcium from bone or is merely a consequence of the regressive changes in bone remains unanswered at present.

RELATION OF THE PARATHYROID GLANDS TO CERTAIN DISORDERS OF NUTRITION—OSTEOMALACIA, OSTEOPOROSIS, OSTEITIS FIBROSA, ETC.

The reproduction of generalized osteitis fibrosa cystica by Jaffé and his co-workers has added significance to the frequent coincidence of this disease with parathyroid hyperplasia. The significance of this coincidence appears further enhanced by the fact that increase in serum calcium, decrease in serum phosphorus and a negative calcium balance have been found in these cases by a number of investigators (Barr, Bulger and Dixon [42]; Hannon and others [43]; Bauer and others [44]). It appears that as a rule only one or several of the parathyroid glands show hyperplasia. On the whole, the microscopic structure of the hyperplastic gland does not deviate from that of the normal gland. However, it is frequently noted that only a small number of fat granules are present in the hyperplastic gland—a finding that is analogous to that in cases of osteomalacia and that is physiologically typical for the parathyroid gland of the new-born infant (Molineus [45]).

While several observers found in the hyperplastic glands irregularities of the cellular architecture suggestive of atypical proliferation, (Paltauf,[46] Wellbrock [47]), it is noteworthy that in no case of osteitis fibrosa has a neoplastic nature of the enlargement of the gland been demonstrated beyond doubt. We are confronted here with the same difficulty as with other endocrine glands. The neoplastic nature, e. g., of adenoma of the thyroid gland, like that of adenoma of the parathyroid glands, has never been proved and has even been refuted. If a tumor distictly differs histologically from the normal parathyroid gland, and if a normal parathyroid gland is present in addition to the tumor,

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41. Robison: Biochem. J. **17**:286, 1923; **20**:388, 1926.
42. Barr; Bulger, and Dixon: J. A. M. A. **92**:951, 1929; Am. J. M. Sc. **179**: 449, 1930.
43. Hannon; Shorr; McClellan, and DuBois: J. Clin. Investigation **8**:215, 1930.
44. Bauer; Albright, and Aub: J. Clin. Investigation **8**:225, 1930.
45. Molineus: Arch. f. klin. Chir. **101**:333, 1913.
46. Paltauf: Zentralbl. f. allg. Path. u. path. Anat. **24**:959, 1913.
47. Wellbrock: Endocrinology **13**:285, 1929.

then the latter may justly be referred to as an "adenoma." Such cases have been observed but rarely.

Hoffheinz,[48] reviewing cases of enlargement of the parathyroid glands, found generalized osteitis fibrosa to have been present in seventeen, and osteomalacia in eight, of forty-five cases. It appears, then, that parathyroid hyperplasia is associated with generalized osteitis fibrosa cystica or with osteomalacia in about 50 per cent of the cases. On the other hand, osteitis fibrosa cystica occurs frequently without parathyroid hyperplasia, as was pointed out by Stenholm.[49] In but two of nine cases of this bone disease did Stenholm find hyperplasia of one of the parathyroid glands. On consideration of the fact that the incidence of parathyroid hyperplasia is higher in cases of osteitis fibrosa and osteomalacia than in normal persons of corresponding age, it is safe to infer that some pathogenic relationship exists between parathyroid hyperplasia and those general bone diseases. In regard to the nature of this pathogenic relationship, the anatomic facts allow one to infer that parathyroid hyperplasia does not necessarily lead to the disorders of the bones referred to. Its rôle in the pathogenesis of osteitis fibrosa cystica and of osteomalacia is evidently dependent on further causative factors and may possibly be dispensable.

Jaffé and his co-workers proved in experiments on animals that an excess of parathormone in the blood may lead to osteitis fibrosa cystica. It is, of course, not permissible to conclude from these experiments that an excess of parathormone is the only etiologic factor in osteitis fibrosa cystica. The effect of parathormone on the calcium metabolism of bones depends in part on the total intake of calcium, on the amount of calcium present in the food and on an adequate supply of vitamin D. The interdependence of these three factors, parathormone, supply of vitamin D and intake of calcium, in their effect on the calcium metabolism has been demonstrated by a number of investigators previously referred to (Hunter and Aub,[33] Morgan and Garrison [34]). A primary disturbance of any one of these factors may lead to a secondary disturbance of either of the other two. Inadequate calcium intake has, with Bauer, Aub and Albright,[35] led to decreased density of bones; with Marine,[50] Sorour [51] and Luce,[52] it has been followed by the appearance of parathyroid hyperplasia.

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48. Hoffheinz: Virchows Arch. f. path. Anat. **256**:705, 1925.

49. Stenholm: Pathologisch-anatomische Studien über die Osteodystrophia fibrosa, Uppsala, 1924.

50. Marine: Proc. Soc. Exper. Biol. & Med. **11**:117, 1913.

51. Sorour: Beitr. z. path. Anat. u. z. allg. Path. **71**:467, 1923.

52. Luce: J. Path. & Bact. **26**:200, 1923.

Chicks growing in light from which the ultraviolet portion has been removed acquired, in the experience of Higgins and Sheard,[53] hyperplasia of the parathyroid glands. Administration of cod liver oil prevented this hyperplasia. In view of these experimental data it appears possible that osteomalacia, osteitis fibrosa and related bone diseases are sequelae of a primary metabolic disorder involving the intake of calcium or the supply of vitamin D, or both of these factors. Hyperparathyroidism may then be a link in a chain of events starting with a primary metabolic disorder and finally leading to the characteristic picture of osteitis fibrosa cystica. Whether in the pathogenesis of osteitis fibrosa cystica, hyperparathyroidism is an indispensable or dispensable link—a reciprocal aggravating effect—remains unanswered at present.

In view of the frequent association of osteitis fibrosa cystica with parathyroid hyperplasia, removal of the hyperplastic parathyroid glands has been suggested as a therapeutic procedure. A consensus apparently prevails in regard to the immediate beneficial effect of the operation. A drop of the serum calcium to or below the normal level regularly ensues, and the patient's general condition improves. A diversity of opinion, however, exists as yet in regard to the permanence of this effect. Mandl,[54] who was the first to perform parathyroidectomy in a case of osteitis fibrosa, reported that three and one-half years after the operation the patient was able to walk on crutches and was free from pains. His serum calcium, however, was from 13 to 14 mg. per hundred cubic centimeters, and the x-ray pictures did not show increased density of the bones.

Improvements of lesser duration have since been reported by several workers (Dubois, quoted by Wilder[55]) even subsequent to the removal of normal-appearing parathyroid glands. Wilder,[55] in a case of diffuse fibrous osteitis, saw rapid improvement after removal of an adenoma of a parathyroid gland. Eighteen months later, like Mandl, he noticed that the density of the bones was still far from normal. The dependence of the disease on other than purely endocrine factors was strikingly suggested in Wilder's case: When the therapeutic use of cod liver oil and calcium phosphate was discontinued, the condition of the patient again became worse. Wilder arrived at the inference that his patient was "still suffering from the same disease." One may conclude that the pathogenic importance of hyperparathyoidism for osteitis fibrosa cystica, as indicated by the experiments of Jaffé and others, has been corroborated by the beneficial effects of the removal of enlarged parathyroid glands in this disease. Therapeutic experience has, how-

53. Higgins and Sheard: Am. J. Physiol. **85**:299, 1928.
54. Mandl: Arch. f. klin. Chir. **143**:1, 1926.
55. Wilder: Endocrinology **13**:231, 1929.

ever, not decisively proved the primary etiologic rôle of hyperparathyroidism in diffuse osteitis fibrosa cystica.

The problem of the sequelae of hyperactivity of the parathyroid glands has been found to be of importance in regard to the pathogenesis of several other diseases of the osseous system. Rats affected with spontaneous rickets were studied by Erdheim.[56] He prepared wax models of the parathyroid glands of these animals and observed a marked enlargement of all these glands. The author interpreted this parathyroid hyperplasia as a consequence and not as as the cause of the bone disease. Ritter,[57] studying the parathyroid glands in twelve cases of human rickets, observed hyperemia, edema and sometimes an increase in fibrous tissue. In cases of long duration he found the glands enlarged, but not in more acute cases. These results, like those of Erdheim, pointed to the parathyroid enlargement as a sequel rather than as a cause of rickets. Some workers were unable to find any change of the parathyroid glands in human rickets.

In five of six cases of osteomalacia, Erdheim [58] found either general or focal hyperplasia of the parathyroid glands. He laid stress on the fact that hyperplastic areas, like the parathyroid glands of the newborn infant, contain scarcely any fat granules. Owing to this scarcity of fat, the newly formed glandular tissue stands out clearly from the adjoining parathyroid substance. Erdheim's findings have been corroborated by others. Todyo [59] found hyperplasia of the parathyroid glands in six of seven cases. Among twenty-four control cases he found the hyperplasia four times. Todyo arrived, as Erdheim had done, at the conclusion that in osteomalacia parathyroid hyperplasia is a sequel probably of increased functional demands on the gland.

In all of nineteen cases of senile osteoporosis, Danisch [60] found focal parathyroid hyperplasia; in a control series of twenty-eight cases of the same age group, he found this hyperplasia but occasionally. Enlargement of parathyroid glands has also been reported in cases of "hunger-osteopathy" (Schmorl [61]).

The association of osteitis fibrosa deformans (Paget's disease) with hyperplastic processes in the parathyroid glands has repeatedly been pointed out (e. g., Maresch [62]). This association is not a regular one,

56. Erdheim: Denkschr. d. k. Akad. d. Wissenschaft. math.-naturw. Kl. **90**:363, 1914.

57. Ritter: Frankfurt. Ztschr. f. Path. **24**:137, 1920.

58. Erdheim: Sitzungsb. d. k. Akad. d. Wissenschaft. math.-naturw. Kl. **116**: 311, 1907.

59. Todyo: Frankfurt. Ztschr. f. Path. **10**:219, 1912.

60. Danisch: Klin. Wchnschr. **3**:1836, 1924.

61. Schmorl: München. med. Wchnschr. **67**:1277, 1920.

62. Maresch: Frankfurt. Ztschr. f. Path. **19**:159, 1916.

as cases of osteitis fibrosa deformans without any macroscopic or microscopic changes of the parathyroid glands have been observed (Hartwich [63]). The frequent but not regular coincidence of bone diseases with parathyroid hyperplasia serves to strengthen Erdheim's contention that the latter is not the primary cause of the former.

SUMMARY

Early experimental work furnished proof of a causal relationship between total parathyroidectomy and tetany and led to the establishment of the symptom complex known as tetania parathyreopriva. Subtotal parathyroidectomy was found to be followed by a state of latent tetany. It has been conclusively shown that tetania parathyreopriva is dependent on lowering of the calcium ion concentration in the serum and, probably, in the central nervous system. When, subsequent to parathyroidectomy, certain protein split products, the guanidines, were found to appear in increased quantity in the urine, some investigators were led to suspect a causal relationship between a derangement of the intermediate protein metabolism and tetany.

This view received support by reason of the similarity in symptoms existing between experimental guanidine poisoning and tetania parathyreopriva. It was thought that an increased effect of guanidines, through the resulting alkalosis, would lead to decrease of the calcium ion concentration. The question remains unanswered whether parathyroidectomy affects the calcium metabolism of the organism directly, or indirectly through an effect either on the intermediate protein metabolism or on the level of inorganic phosphorus in the serum.

Parathyroid function was found to be of importance in regard to the formation, the maintenance and the repair of bone as well as in regard to the formation of teeth. Incomplete calcification of regenerating teeth, incomplete, delayed calcification of the callus of fractured bones and decreased calcium storage of bones ensue from parathyroidectomy. The presence of an excessive amount of the specific hormone of the parathyroid glands in the blood, on the other hand, may also lead to decrease of the calcium content of the bones. In this case, the hypercalcemia resulting from the excessive parathormone content of the serum appears to be induced at the expense of the calcium of the bone.

Recent experimental work has clearly indicated that the effect of the parathyroid hormone depends on the total intake of calcium as well as on the supply of vitamin D. This interdependence of three factors influencing the calcium metabolism appears to be of considerable significance in regard to the pathogenesis of generalized osteitis fibrosa

63. Hartwich: Virchows Arch. f. path. Anat. **236**:61, 1922.

cystica, osteomalacia, osteoporosis and related bone diseases. These bone diseases are frequently associated with hyperplasia of the parathyroid glands. However, they occur in a good many instances without parathyroid hyperplasia, and again, the latter occurs without the bone diseases under consideration.

Such facts render it unlikely that hyperparathyroidism is the sole cause of osteitis fibrosa and the related bone disorders. On the contrary, they suggest that in the pathogenesis of these diseases hyperparathyroidism is not the primary etiologic factor. In apparent contrast to this inference stands the experimental reproduction of osteitis fibrosa cystica through repeated injections of parathormone. When one considers that disturbance of either the intake of calcium or of the supply of vitamin D may secondarily lead to hyperparathyroidism, it becomes possible to reconcile the anatomic and the experimental data available.

A primary metabolic disorder, concerning the intake of calcium or the supply of vitamin D, or both, may lead to a disturbance of the calcium storage of the bones. Simultaneously it may lead to a hyperactivity of the parathyroid glands. The latter, in turn, may result in lesions characteristic of osteitis fibrosa cystica, depending, however, again on the intake of calcium and the supply of vitamin D. At present, it remains an open question whether in the pathogenesis of osteitis fibrosa cystica hyperparathyroidism is an indispensable etiologic factor —as suggested by experimental results—or a secondary aggravating phenomenon.

Notes and News

University News, Promotions, Resignations, etc.—James Ewing, formerly professor of pathology at Cornell University Medical College, has been appointed director in full charge of the Memorial Hospital for the Treatment of Cancer and Allied Diseases. Recently Dr. Ewing was awarded the honorary degree of Sc.D. by the University of Rochester.

George Washington University has conferred the honorary degree of doctor of science on F. P. Gay, professor of bacteriology in Columbia University.

Frank L. Apperly, recently of the department of pathology in the University of Melbourne, has been appointed professor of pathology in the Medical College of Virginia at Richmond.

George W. Bachman has been appointed director of the School of Tropical Medicine of Columbia University, San Juan, Porto Rico.

Frank B. Mallory, pathologist to the Boston City Hospital, has been awarded the honorary degree of doctor of science by Boston University.

The doctorate of science was conferred recently by Colgate University on S. A. Petroff, director of the laboratory of Trudeau Sanitarium.

Society News.—The Ninth International Congress of the History of Medicine will meet in Bucharest on Sept. 10 to 18, 1932.

The Society for Experimental Biology and Medicine recently elected A. R. Dochez, president; E. L. Opie, vice president; A. J. Goldforb, secretary-treasurer.

At its last annual meeting in New Orleans, the American Society of Clinical Pathologists gave the Ward Burdick award to Benjamin S. Kline, Cleveland, Ohio, for work on the serological diagnosis of syphilis. R. R. Kracke was awarded the gold medal for his demonstration of agranulocytic angina in the scientific exhibit of the society. A. J. Foord is the president-elect.

Tumor Clinic in the Edward Hines Veterans' Hospital.—Approximately 200 beds are now devoted to cancer patients. Two and one-half grams of radium are available. In 1931 more than a thousand patients with neoplasms were under treatment. It is estimated that among 4,500,000 veterans neoplasms will develop in approximately 9,000 in 1932; further, that in 1942, when the number of veterans will be about 4,000,000, about 17,000 will have tumors.

Manson Medal.—According to *Science*, the Manson medal for tropical medical research, given triennially by the Royal Society of Tropical Medicine and Hygiene, has this year been awarded to Theobald Smith, who recently retired as director of the department of animal pathology of the Rockefeller Institute for Medical Research. The previous recipients of the Manson medal have been David Bruce (1923), Ettore Machiafava (1926) and Ronald Ross (1929).

Trudeau Medal.—"For outstanding service to the tuberculosis movement," the National Tuberculosis Association has awarded the Trudeau Medal to Esmond R. Long, until recently professor of pathology in the University of Chicago and now professor of pathology in, and director of the laboratories of, the Phipps Institute of the University of Pennsylvania.

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

THE INFLUENCE OF FEEDING OF THYROID GLAND ON TISSUE RESPIRATION. E. ROBLES, Frankfurt. Ztschr. f. Path. **41**:193, 1931.

A series of white mice were fed with dried thyroid tissue and dried portions of the anterior lobe of the hypophysis. Over a period of from five to thirty days, from 0.09 to 0.1 Gm. of the preparation was given by mouth in addition to a diet containing bread, milk and oatmeal. The metabolism of the kidney, liver, lungs and spleen was determined according to the Warburg method. The determination was done twenty-four hours after the last feeding, so as to rule out digestion as a possible factor in explaining increased metabolism. Beginning with the fifteenth day after the introduction of the feeding, there was a distinct increase in tissue respiration. Because of the fact that thyroxine alone does not lead to an increase of tissue respiration, the author concludes that other important hormones were present in the material used in addition to thyroxine.

O. SAPHIR.

THE EXPERIMENTAL PRODUCTION OF AMYLOID BY MEANS OF IMPLANTATION OF ORGANS. J. CRUZ, Frankfurt. Ztschr. f. Path. **41**:250, 1931.

In a number of mice in the abdominal cavities of which parts of various organs of other mice were implanted, amyloid was demonstrated. It was found mainly in the spleen, but also in the kidneys, liver, lungs and heart. If parts of organs taken from guinea-pigs were implanted in mice, amyloid was found much less frequently. The author concludes that the absorption of homologous protein leads to a formation of amyloid more readily than the absorption of foreign protein.

O. SAPHIR.

LOCALIZATION OF LIPOID DEPOSITS. K. LÖWENTHAL, Frankfurt. Ztschr. f. path. **41**:374, 1931.

In mice, after repeated intraperitoneal injections of cholesterol in oil (a 3 per cent solution of cholesterol in peanut oil) fat emboli were found in the lungs and other organs, in addition to lipoid deposits in the endothelial cells of the blood vessels. Repeated intraperitoneal injections of neutral fats, however, led to the formation of fat emboli, but did not produce intracellular deposits of fats. Also, after subcutaneous injection of cholesterol in oil, deposits of lipoid could be demonstrated.

O. SAPHIR.

THE RESORPTION AND EXCRETION OF LIPOIDS AFTER A SINGLE ADMINISTRATION. M. LEFFKOWITZ, Frankfurt. Ztschr. f. Path. **41**:386, 1931.

In 55 mice, cholesterol in oil (5 per cent solution of cholesterol in peanut oil) was given either by mouth once or by one intraperitoneal injection. When such a lipoid was given per mouth, it reached the liver, was kept there, and was not found in the lungs or kidneys. When the cholesterol was injected intraperitoneally, it was brought by the thoracic duct into the lungs and was also found occasionally in the kidneys. In castrated mice, lipoids might also be present in the kidneys, following the feeding with cholesterol.

O. SAPHIR.

AUTOTRANSPLANTATION OF SPLENIC TISSUE. W. PUTSCHAR, Verhandl. d. deutsch. path. Gesellsch. **26**:259, 1931.

In twenty-four rats, the spleen was removed and reimplanted in three or four small pieces; in seventeen animals, these pieces of splenic tissue were placed in the peritoneal cavity; in seven, in the subcutaneous tissue of the abdominal wall. Twelve rats survived this operation for from four to five months. Only in two animals was the transplantation unsuccessful. Histologic examination of the grafts revealed living, functioning tissue. In half of the surviving cases, typical malpighian bodies were found in the transplanted pieces.

C. ALEXANDER HELLWIG.

THE RELATIONSHIP BETWEEN NODULES OF THE THYROID GLAND AND PREGNANCY. H. SCHLEUSSING, Verhandl. d. deutsch. path. Gesellsch. **26**:304, 1931.

The examinations were made in Düsseldorf, in the lower Rhine Valley, where goiter is not endemic. The incidence of nodules in thyroid glands of normal size was determined in 276 women more than 20 years old. The incidence and number of nodules increased with the number of childbirths. Of women without children, 25 per cent had nodules; of those with one childbirth, 40.4 per cent. The rate of incidence increased to 100 per cent in women with more than ten childbirths. In the latter group, all had more than one nodule in the thyroid gland. In pregnancy, the activity of the thyroid gland is increased; the resulting diffuse hyperplasia favors the development and growth of nodules.

C. ALEXANDER HELLWIG.

INTRACRANIAL PRESSURE IN ITS RELATION TO THE HYPOPHYSIS AND CYSTIC OVARIES. J. KRAUS, Verhandl. d. deutsch. path. Gesellsch. **26**:308, 1931.

In 45 of 50 patients with increased intracranial pressure due to a chronic process, the weight of the hypophysis was greater than normal. Microscopically, cellular hypertrophy and hyperplasia were found, especially of the principal cells in the anterior lobe. Only those showed hyperplasia in which the infundibulum and the floor of the third ventricle were intact. The cause of this enlargement is entirely unknown. In patients with metastases of malignant tumors in the brain and with chronic abscesses of the brain the weight of the hypophysis was not increased. In 83 per cent of the women of the series there was a small cystic degeneration of the ovaries. Since in several men and women with tumors of the brain causing intracranial pressure, the pituitary hormone was found increased in the urine, and since the injection of the hormone into animals causes cystic degeneration of the ovaries, there seems to be a relationship between the described changes in the hypophysis and the cystic degeneration of the ovaries.

C. ALEXANDER HELLWIG.

THE EFFECT OF SODIUM HEXOSEDIPHOSPHATE ON DIABETIC AND NORMAL ANIMALS. W. S. ILYIN and J. T. KUSNETZOW, Ztschr. f. d. ges. exper. Med. **79**:635, 1931.

The injection of sodium hexosediphosphate into a depancreatized animal causes a sharp and moderately lasting drop in the blood sugar, often to normal, and a rise in the inorganic phosphates of the blood. The level of the blood sugar in a normal animal is not affected by the injection of this substance. In certain experiments on diabetic animals with the sodium hexosediphosphate there occurred a reaction that was controlled by the use of ether; the drop in blood sugar, however, remained constant. Synthetic sodium glycerophosphate, injected subcutaneously, acts in the same way in diabetic as in normal animals in splitting off inorganic phosphate. Large doses of sodium glycerophosphate are toxic. Injection of the latter substance not only in small but also in large doses has no depressing effect on the

level of the blood sugar, even though the phosphate content of the blood rises. More exact knowledge of the part of phosphate, as well as of the complex esters of phosphoric acid, awaits further investigation.

FROM THE AUTHORS' SUMMARY.

STUDIES ON THE THYROID GLAND. H. OKKELS, M. KROGH and A. LINDBERG, Acta path. et microbiol. Scandinav. **9**:1, 21, 37, 1932.

Histology and Cytology of the Normal and Abnormal Human Thyroid Gland (H. Okkels).—The mitochondria appear to show some relation to the production of colloid, and as a rule their number is increased in cases of exophthalmic goiter treated with iodine. The Golgi apparatus is distinctly hypertrophic in exophthalmic goiter, but its position in the cell has nothing to do with the direction of the secretion to either side, into the alveolus or into the capillary. There is no cytologic or histologic reason to assume that in exophthalmic goiter the thyrotoxicosis is due to anything else than an excessive hypersecretion into the blood stream, preventing the accumulation of colloid. Preoperative treatment with iodine, while for a time reducing the toxic symptoms and inducing an accumulation of colloid, does not influence the marked hypertrophy of the Golgi apparatus, and the cellular hyperactivity probably keeps on unabated. It is logical, therefore, to assume that the factor inducing this hypersecretion must be some extrathyroid principle, and if so, it must be a stimulant of nervous or humoral character.

Physiologic Activity of Iodine in Thyroxine and in the Normal and Pathologic Thyroid Gland (M. Krogh and A. Lindberg).—The biologic activity of thyroxine, dried thyroid gland of the guinea-pig and resected human thyroid gland on the metabolism of full grown male guinea-pigs has been compared by feeding doses corresponding, in each case, to 4.5 mg. of iodine per square millimeter of surface every other day for two weeks and measuring daily the resting metabolism at from 31 to 32 C. The activity of thyroxine is about two thirds that of dried thyroid gland of the guinea-pig. The iodine content of human thyroid gland varies greatly; in simple goiters, it is between 0.04 and 0.4 per cent; in exophthalmic goiters that have not been treated with iodine, between 0.03 and 0.07 per cent, and in iodine-treated exophthalmic goiters, between 0.03 and 0.4 per cent. The dried glands from simple goiters and from exophthalmic goiters successfully treated with iodine brought about an increase in metabolism of nearly the same magnitude as that caused by the normal guinea-pig's thyroid gland. Glands from nontreated exophthalmic goiters and from iodine-treated ones in which the treatment was ineffective both clinically and histologically showed a biologic activity per milligram of iodine markedly below the normal. The most probable explanation appears to be that in thyroid glands that are unable to store the hormone, giving it off to the blood as rapidly as it is formed, the intermediate products between inorganic iodine and the final hormone may make up a significant fraction of the total iodine, which probably is not the case in normal glands or in colloidal goiters.

Experimental Hyperactivity of the Thyroid Gland (M. Krogh, A. Lindberg and H. Okkels).—Extracts from the anterior lobe of the pituitary gland injected subcutaneously into young or full-grown guinea-pigs induce hyperactivity of the thyroid gland. As reliable criteria of hyperactivity of the thyroid gland after injection of the aforementioned extracts we found the following phenomena: 1. Considerable increase of the standard metabolism and pronounced hypertrophy of the Golgi apparatus in the thyroid gland cells, generally parallel with the increase in the metabolism. These experiments therefore establish the fact that the Golgi apparatus is an indicator of specific cellular activity. 2. Marked proliferative changes in the thyroid gland, with hypertrophy of the gland cells, increased vascularization and marked diminution of the colloid content. In pronounced cases, the microscopic changes in the gland are of such a nature and degree that they cannot be distinguished from those of human exophthalmic goiter. Peroral administration of the alkaline extract showed no effect. Subcutaneous injection of sex

hormone preparations of the anterior lobe of the hypophysis gave perhaps a slight decrease in the standard metabolism, but no structural changes in the thyroid gland. Peroral administration of large doses of dried thyroid gland or subcutaneous injection of thyroxine solution daily for up to one week produced a considerable increase in the metabolism, but no change in the thyroid gland. Peroral administration of dried thyroid gland in full-grown guinea-pigs for a period of eight months produced an increased accumulation of colloid in the alveoli and a slight degree of atrophy of the lining cells in the thyroid gland.

AUTHORS' SUMMARIES.

MAMMALIAN PARABIOSIS, WITH PARTICULAR REFERENCE TO THE SEX GLANDS AND THE HYPOPHYSIS. E. MÖLLER-CHRISTENSEN, Acta path. et microbiol. Scandinav. **9**:55, 1932.

This is a general review of experimental mammalian parabiosis, with bibliography.

Pathologic Anatomy

HISTOLOGIC STUDIES OF THE BRAIN IN CASES OF FATAL INJURY TO THE HEAD. C. W. RAND and C. B. COURVILLE, Arch. Surg. **23**:357, 1931.

This study was directed to determining the changes occurring in the choroid plexus and the ependymal lining of the ventricles in fatal cases of traumatic injury to the head. Sixty-one brains in such cases were studied, along with ten normal brains as controls. Following trauma, definite changes occur in the choroid plexus. The free epithelial margin becomes irregular in outline, and the cells increase in height. Occasionally, the free epithelial margin is ragged and torn, and free fragments are found in the ventricular space. Vacuolization of the epithelial cells is prominent. Granulation of the cytoplasm is present and varies in amount, being more or less proportionate to the size and swelling of the cells. The nuclei become swollen and vesicular; occasionally, they are ruptured. Sometimes the nuclei shrink, and the chromatin becomes condensed. Autochthonous pigment is occasionally increased and is usually distributed in the periphery of the vacuoles. This pigment does not stain for iron. The basement membrane is sometimes torn, and fluid collects between it and the cells. The connective tissue stroma becomes prominent by virtue of edema, and this edema probably precedes the vacuolization in the cells. The changes in the ependymal epithelium are similar, but are rather less marked than those in the choroid. Subependymal edema is rather prominent. Increased vacuolization of the epithelium of the choroid and of the ependyma suggests that these cells actively secrete fluid, and it seems logical to conclude that following injury to the brain their activity is increased. This would account for the increased cerebrospinal fluid found in injuries to the brain. In those cases in which hypertonic dextrose was given intravenously shortly after the injury, the changes in the choroid plexus and the ependyma were less marked. In general, it may be stated that the changes noted in these fatal cases resemble experimental "water brain" of animals produced by intravenous injection of hypotonic solution.

N. ENZER.

THE TYPICAL POSITION OF THE MYOCARDIAL SCARS FOLLOWING CORONARY OBSTRUCTION. W. G. MACCALLUM and J. S. TAYLOR, Bull. Johns Hopkins Hosp. **49**:356, 1931.

Three typical photographs from a large series are reproduced to show the contrast between obstruction of the anterior descending branch of the left coronary artery, obstruction of its circumflex branch and obstruction of the right coronary artery. Obstruction of the anterior descending branch usually results in scarring of the more anterior part of the interventricular septum, sometimes even extending though to the right ventricle, and of the apical and more anterior part of the wall of the left ventricle. Obstruction of the left circumflex branch

results in scarring and thinning of the wall of the left ventricle in its more median portion between the area of the left anterior descending branch and that of the right coronary. Obstruction of the right coronary artery, especially of the distal portion, produces dilatation and a scar that begins in the midline of the interventricular septum and extends backward behind the papillary muscles of the mitral valve to curve around on the most posterior part of the wall of the left ventricle. Scarring of the wall of the right ventricle is rare, and this may be due to the more direct course of the branches of this artery that supply it. If these anatomic changes are kept in mind, one can tell, from the position of the scarred area, which coronary artery is obstructed.

LUKE HUNT.

LESIONS IN THE LATERAL HORNS OF THE SPINAL CORD IN ACRODYNIA, PELLAGRA AND PERNICIOUS ANEMIA. S. T. ORTON and L. BENDER, Bull. Neurol. Inst., New York **1**:506, 1931.

The lesions of the central nervous system in one case of acrodynia, one case of pellagra and five cases of pernicious anemia are described. In all the cases we have found severe lesions in the lateral horns of the lumbar and thoracic levels of the spinal cord and analogous areas at other levels. These lesions are all of a chronic type, characterized by loss of nerve cells and nerve fibers and by fibrous glial replacement. Since the lateral horn region contains the cell bodies of the effector neurons that serve to connect the spinal cord with the sympathetic nervous system, lesions in this locus are held to be in suggestive relation to the disturbances of vasomotor and splanchnic control which are common to these diseases.

AUTHORS' SUMMARY.

THE RELATIONSHIP OF THE SUBARACHNOID AND PERINEURAL SPACES. C. G. DYKE and E. M. DEERY, Bull. Neurol. Inst., New York **1**:593, 1931.

A woman received an intraspinal injection of iodized poppy seed oil 40 per cent, which on roentgenologic examination was found scattered throughout the subarachnoid space from the fifth dorsal to the fourth lumbar vertebrae. At the sixth, seventh and tenth dorsal segments the iodized oil could be seen emerging from the intervertebral foramina; some was seen far out from the boundaries of the vertebral canal, and in the lumbar region rather large collections of iodized oil were seen outside the canal boundaries. "The distribution closely resembled the arrangement of the lumbar sacral plexus." In short, the iodized oil traveled from the subarachnoid space along the perineural spaces of the lumbosacral nerves; hence these spaces may be avenues of escape for arachnoid fluid.

GEORGE B. HASSIN.

ABSENCE OF THE CERVICAL SPINE (KLIPPLE-FEIL SYNDROME). G. I. BAUMAN, J. A. M. A. **98**:129, 1932.

The Klipple-Feil syndrome is a numerical variation in the cervical vertebrae, with more or less complete fusion into one mass accompanied in some cases with spina bifida or other anomalies. Only thirty cases have been reported, mostly in the French literature. Six cases of this anomaly are reported by Bauman. In all of the cases there was marked diminution in the number of cervical vertebrae, and those remaining were fused into one mass. Some of the cases presented lesions of nerves, and the question has been raised as to whether the original lesion is in the nervous or in the osseous system. One symptom present in four of the cases was an inability to dissociate the movements of the two hands. Any movement performed by the right hand was copied more or less accurately by the left. The phenomenon has been designated the mirror movement. The classic symptoms as observed by Klipple and Feil are absence or shortening of the neck, lowering of the hair line on the nape of the neck and limitation of motion. Other symptoms occurring in a certain percentage of cases are torticollis, mirror move-

ment, facial asymmetry, dorsal scoliosis, other deformities, difficulty in breathing or swallowing and shortness of breath. Changes in individual muscles have been noted. Muscle spasm or almost constant contraction of the cervical muscles has been observed and explained on the assumption that the muscles must take the place of the osseous system in supporting the head. The neck is so short that the thorax almost reaches the head, Klipple and Feil referring to this as the cervical thorax. The deformity remains stationary. It is disguised with difficulty and unfortunately does not become less conspicuous as the patient develops. The mirror movement, when present, become less noticeable, but does not disappear. The deformity does not interfere with longevity. No treatment is of benefit. Operations should be avoided by the making of a correct diagnosis.

LUKE W. HUNT.

RUPTURE OF THE CORONARY ARTERY. C. B. BAMFORD, Brit. M. J. **1**:842, 1931.

Two cases are reported. In one, which concerned a patient with dementia praecox, aged 64 years, the features of interest were the presence of multiple aneurysms of the coronary arteries, situated in an unusual position—namely, toward the terminal parts of the artery rather than near the place of origin; the rupture of one of these aneurysms into the pericardium; the condition of the aorta, suggesting a probable syphilitic origin of the aneurysms. In the second case, which concerned a patient with dementia, aged 69 years, the rupture of the coronary artery was the end-result of advanced arterial degeneration, associated with chronic renal disease and cardiac hypertrophy.

SACCULATED ANEURYSM OF THE MIDDLE CEREBRAL ARTERY. W. H. CHASE, J. Path. & Bact. **35**:19, 1932.

A large, sacculated, ruptured aneurysm has been described on the right middle cerebral artery at the position of its cortical branches, and lying entirely within the right cerebral hemisphere. Histologic and anatomic study of the intracranial vessels suggests that the aneurysm developed as the result of a congenital defect in the wall of the vessel at a point of branching.

AUTHOR'S SUMMARY.

POLYPI COLI. W. SUSMAN, J. Path. & Bact. **35**:29, 1932.

Polypi coli were found in 6 per cent of 1,100 necropsies. No preference for any particular segment of the colon was noted. In about one half of the cases of carcinoma, coli polypi coexisted, and in about one third of this group there were malignant polypi. Of the 66 cases showing polypi coli, 15, or about one-fourth, were also cases of carcinoma coli. Polypi coli occurred most commonly in males, and in persons in later adult life. Only 7 per cent of those affected were under 40 years.

AUTHOR'S SUMMARY.

CAPILLARY HAEMANGIOMA OF THE SPINAL CORD ASSOCIATED WITH SYRINGOMYELIA. D. S. RUSSELL, J. Path. & Bact. **35**:103, 1932.

A case is described in which a capillary hemangioma (hemangioblastoma) of the cervical enlargement was associated with syringomyelia.

AUTHOR'S SUMMARY.

CARDIAC BERIBERI OF NURSLINGS. J. ALBERT, Hyg. soc. **60**:1008, 1931.

Infantile beriberi is responsible for 28 per cent of deaths of infants under 1 year of age in the Philippines. Of the three forms (aphonic, pseudomeningitic and cardiac) the last is the most serious. At autopsy there are cardiac hypertrophy and dilatation (often only of the right side of the heart), diffuse congestion of

the viscera and anasarca. A degenerative neuritis of the vagus occurs with long duration of the disease. The malady is observed always in an infant between 1 and 3 months of age, nourished by a mother suffering from latent or "partially apparent" beriberi. The infant is generally well developed, often large, and considered in good health.

H. S. THATCHER.

LYMPHOGRANULOMATOSIS. TITU VASILIU et al., Presse méd. **40**:25, 1932.

This is the report of a session of the Société anatomique devoted to lymphogranulomatosis. The disease is generally accepted to be an infectious granuloma, but the tuberculous etiology is rejected. Bezançon reports that inoculations of tissue into animals have occasionally given rise to generalized adenopathies transmissible in series. The lymph nodes contained many eosinophils, but no organisms could be detected. Cornil in the same manner obtained reticular changes and microscopic abscesses in the spleen, which appeared after intervals of three, four and nine months. The wide variations in the histologic picture of Hodgkin's disease are emphasized, pseudoneoplastic, inflammatory and plasmocytic forms being described. All of the cell forms are traced to the hemohistioblast of Ferrata. Some authors have attempted to identify the Reed-Sternberg cell with the megalokaryocyte of the marrow on the basis of the morphology and the high platelet count. No essential distinction is believed to exist between the typical form of the disease and those showing extensions to the lungs and pleura, the bones and the skin. The spleen is involved in 95 per cent of the cases. Henschen calls attention to certain rare generalized hyperplasias of the reticulo-endothelial system that defy interpretation. They have been termed histiocytosis, endotheliosis and reticulosis.

A. F. DEGROAT.

THE GENESIS OF HYALINE BODIES IN TISSUES. F. PESCATORI, Sperimentale, Arch. di biol. **85**:25, 1931.

Study of hyaline bodies found in chronic inflammatory and in neoplastic tissues, especially of the gastric wall, suggests that they are almost always situated in the submucosa, and that their formation depends on atrophy of the epithelial or muscular tissues. Another possible explanation of their formation is an altered local metabolism that results in the accumulation of the products of metabolism in the tissues.

G. PATRASSI.

SKELETAL CONDITIONS IN CRANIORACHISCHISIS AND CRANIOSCHISIS. E. GIERKE, Centralbl. f. allg. Path. u. path. Anat. **53**:1, 1931.

Gierke studied the skeletal and particularly the cranial alterations in a craniorachitic and an anencephalic monster and compared them with normal fetuses 17 cm. and 46 cm. in length. He made paper models of the occipital bone, and by flattening or bending these he was able to approximate conditions found in the deformities in question. He is of the opinion that pressure of some sort is the cause of these arrests in development, but offers no suggestion as to the origin of such pressure.

GEORGE RUKSTINAT.

THE ETIOLOGY OF BLOOD CYSTS FOLLOWING HEMORRHAGIC PACHYMENINGITIS. L. HARANGHY, Centralbl. f. allg. Path. u. path. Anat. **53**:65, 1931.

In the body of a 25 year old male idiot, blind since the age of 1½ years, were found two huge cysts of the dura, partially calcified and communicating with one another. These cysts were separated in front for 8 cm., but communicated posteriorly through a 10 cm. aperture in the falx cerebri. The depth of the cyst on the right side was 5.5 cm. at the coronal suture, and 10 cm. at the place of greatest pouching in the parietal region. The left cyst was about 2 cm. smaller at these respective places. The cysts contained 1,100 cc. of orange-colored fluid in which

were suspended crystals of cholesterol. The brain was markedly flattened. The development of these cysts in the dura is ascribed to trauma at birth in which the falx cerebri was torn, providing a connection between the two sides of the skull. Hemorrhagic pachymeningitis then developed and later partial calcification of the of the wall of the cyst. Death was due to gangrene of the right lung and pleurisy.

GEORGE RUKSTINAT.

THE ETIOLOGY OF LIPOGRANULOMATOSIS. W. J. SCHLAPABERSKY, Centralbl. f. allg. Path. u. path. Anat. **53**:97, 1931.

The author reports investigations of a region of lipogranulomatosis, 20 cm. long, about and proximal to the right knee of a tabetic patient who died of phlegmon of the thighs and retroperitoneal tissues. Histologically, this region contained many cysts filled with clear fluid and having walls composed of concentric layers of hyalinized connective tissue. Some portions of the walls were calcified, and some of the cavities contained fat droplets and crystals, which were thought possibly to be fatty acids. About the right knee joint there were evidences of resorption of bone. The author comments on the classification of lipogranulomatosis suggested by Abrikosoff, and believes that the spontaneous type may possibly be neurogenic. The reason for this belief is furnished in the present report, in which definite evidence is set forth of an atrophy of bone and muscle occurring in tabes. Additional support for such a view is obtained from observations on spotted fever, which is cited as the most common precursor of spontaneous lipogranulomatosis. In this illness, lesions of the nervous system occur and may give rise to neuralgic pain. Another reason for believing neurogenic or trophic disturbances are intimately associated with lipogranulomatosis is the bilateral symmetrical extent of the lesions occasionally seen.

GEORGE RUKSTINAT.

STUDIES OF THE EXTRAHEPATIC BILE DUCTS. J. F. NUBOER, Frankfurt. Ztschr. f. Path. **41**:198 and 454, 1931.

In this extensive study, the author discusses the anatomic and histologic appearances of the extrahepatic bile ducts under normal and pathologic conditions. The article is not suitable for an abstract. For information, the original article must be consulted.

O. SAPHIR.

CONGENITAL LEUKEMIA. W. BÜNGELER, Frankfurt. Ztschr. f. Path. **41**:257, 1931.

Leukemia is reported in a stillborn infant of about seven months' gestation, measuring 39 cm. in length and weighing 1,620 Gm. The liver was enlarged, weighing 125 Gm.; its architecture was completely obscured. Histologically there were large myelocytic infiltrations between the capillaries and the hepatic cells. The cells revealed eosinophilic and neutrophilic granules. Relatively few nucleated red cells were found. The spleen weighed 55 Gm. The follicles were not recognizable. Histologically, a marked infiltration was noted by cells similar to those found in the liver. The architecture of the lymph nodes was obscured. No follicles or germinal centers could be made out. There was a fine reticulum in the meshes of which many myeloid cells were observed. The bone marrow was outspokenly gray, with a few red dots; it showed few erythroblasts and erythrocytes, but many myeloblasts, and neutrophilic and eosinophilic myelocytes. Four fifths of the cells gave a positive oxydase reaction. No iron-containing pigment was noted. Many myeloid cells were found in the myocardium, lungs, kidneys, pancreas, gastro-intestinal tract and skin. At postmortem examination, smears taken from the blood of the vena cava and heart revealed 80 per cent myeloblasts and myelocytes. The author discusses the question of whether this disease is identical with the leukemia of the adult.

O. SAPHIR.

METASTATIC MEDULLARY NECROSIS OF THE KIDNEYS. W. SCHÖMER, Frankfurt. Ztschr. f. Path. **41**:265, 1931.

Three cases of metastatic renal medullary necrosis are described. In one, the necrosis was confined to the medullae of the kidneys; in two, the cortices were also involved. In all three cases, similar bacteria were found in the kidneys and in the spleen. The lesions in the kidneys apparently were secondary to ulcerative endocarditis in one case and to thrombophlebitis as the result of otitis media in a second case. In the third case, there was apparently bacteremia, the port of entry of which could not be detected. An attempt is made to explain the selective necrosis of the media by the peculiar blood supplies of the medulla. O. SAPHIR.

OSTEOGENESIS IMPERFECTA. W. HOF, Frankfurt. Ztschr. f. Path. **41**:306, 1931.

A case of osteogenesis imperfecta is reported in a 5 months old girl. At the time of birth, a fracture of the right forearm, marked bending of both shanks, genu extrorsum and tali pes varus were noted. The child died of bronchopneumonia. The autopsy revealed plump extremities, a large head, multiple fractures, thickenings of the seventh and eighth ribs and internal hemorrhagic pachymeningitis. Both tibiae were markedly curved. The large fontanel was wide open and the skull very thin, with small hemorrhages below the periosteum. The dura was adherent to the skull. An enlargement of the thyroid gland was noted. Histologically, there was marked increase of cartilage throughout the bones, with some calcification. There was only slight formation of bone in the region of the calcified cartilage, in spite of the fact that the many coherent osteoblasts were found close to the epiphysis. The cortical layer was only slight in amount; its lamellated arrangement was missing. The bone marrow was markedly hyperplastic. Cysts filled with homogeneous material were found in the bone marrow. The older fracture revealed much callus, which in part contained cartilage. The author discusses the etiology of this disease, but does not believe that the hyperplasia of the bone marrow was the primary cause. O. SAPHIR.

Microbiology and Parasitology

BACILLUS MUCOSUS INFECTION OF THE NEW-BORN. MARK JAMPOLIS, KATHARINE M. HOWELL, JOSEPH K. CALVIN and M. L. LEVENTHAL, Am. J. Dis. Child. **43**:70, 1932.

An outbreak of infectious diarrhea developed in a nursery for the new-born. The symptoms were striking in severity, and mortality was high. Apparently the offending organism was Bacillus mucosus, the virulence of which may have been enhanced by symbiosis with anhemolytic streptococci. The primary and outstanding pathologic finding in the fatal cases was acute enteritis, the mucous membrane of the ileum being red, swollen, finely granular and covered with reddish-gray mucus. Microscopic examination showed the mucosa to be infiltrated with polymorphonuclear leukocytes and lymphocytes. A few shallow ulcers were found, and the lymphoid tissue was hypertrophied. Cultures from the throats and stools of three nursery maids revealed practically pure cultures of B. mucosus. When these nursery maids were relieved of their duties, the outbreak promptly subsided.

FROM THE AUTHORS' SUMMARY.

BACT. TULARENSE IN THE EASTERN WOOD TICK, DERMACENTOR VARIABILIS. R. G. GREEN, Am. J. Hyg. **14**:600, 1931.

Bacterium tularense has been isolated directly from the eastern wood tick, Dermacentor variabilis, by inoculation of a guinea-pig and subsequent culture. Over an area of 20 square miles in central Minnesota the percentage of wood tick

infection was found to be less than 0.1 of 1 per cent during the summer of 1930. The animal culture derived from ticks was of low virulence as indicated by the type of lesion produced and by failure consistently to produce fatal infections in rabbits.

AUTHOR'S SUMMARY.

OBSERVATIONS ON HOOKWORM DISEASES IN COSTA RICA BASED ON POST-MORTEM FINDINGS. LOUIS SCHAPIRO and E. G. NAUCK, Am. J. Hyg. **14**: 705, 1931.

The point to be emphasized is that the principal seat of the worms is the jejunum, in which are also found the lesions occasioned by the presence of the worms: more or less numerous punctiform extravasations of blood, and catarrhal inflammatory manifestations and edema of the mucosa. In the cases in which hookworm disease was the cause of death, we almost always found the jejunum and duodenum infested. In less intense infestations, frequently only the jejunum contained worms. The ileum, in all degrees of infestation, was most frequently found to be free from worms and only occasionally served as a site of the specimens recovered. According to our experience, the worms, even when they are loosened from the intestinal wall, very often remained alive and mobile for more than twelve hours after the death of the host. Our observations have shown that Ankylostoma duodenale is also more resistant in this respect and remains alive longer than Necator americanus. Extensive bloody infiltration of the mucosa and submucosa is rare, despite the fact that the mucus found on the surface of the mucosa (which is frequently sticky and abundant) may be markedly stained with blood. In none of the bodies dissected did we see signs of severe hemorrhage. The interesting question of the origin of hookworm anemia cannot be settled on the basis of pathologico-anatomic findings alone. It is, however, evident that the worms found at autopsy for the most part contain little or no blood in their intestinal tracts; and except for the punctiform mucosal hemorrhages (sometimes as large as lentils) and an occasional bloody injection of the intestinal contents, no marked hemorrhages are found.

FROM AUTHORS' SUMMARY.

THE BEHAVIOR OF RABBIT VIRUS III IN TISSUE CULTURE. TEODULO TOPACIO and ROSCOE R. HYDE, Am. J. Hyg. **15**:99, 1932.

Of seventy-six Maryland rabbits inoculated with virus III, 83 per cent were susceptible, as compared with 85 per cent reported by Rivers and Tillett in New York, and nearly 100 per cent reported by Miller and Andrewes in England. This refractory state was found in old animals. It is due apparently to an immunity established as a result of the infection. Although our experiments in cultivation in series have shown that the virus was still infective in a dilution of 1: 300,000,000, this is not an absolute proof that the virus had actually multiplied. However, we believe that this occurred. The viability of the virus depends on the presence of living cells in the cultures. A minute anaerobic coccus or diplococcus was seen in normal rabbit testis which in cultures kills virus III. A slight bacterial contamination is tolerated by virus III, but a heavy one destroys it. The virus from tissue cultures is more virulent than that from the animal itself, as judged by the severity of the lesions. Passage of the culture virus from animal to animal apparently adapts it to the animal type. The fluid expressed from the plasma clot of the tissue cultures was infectious as shown by inoculation of animals. We are in agreement with Andrewes on this point. In cultures of rabbit testis, the virus attacks the interstitial cells and never the sex or primary cells as evidenced by the formation of inclusions in the former. All types of interstitial cells are susceptible to the formation of inclusions. Inclusions of virus III form regularly in cultures of normal rabbit testis in normal plasma regardless of whether the tissues are exposed to the virus for ten minutes or for one hour at room temperature. We agree with Andrewes on this point. The presence of inclusions in a tissue culture of virus III indicates that the virus is viable. This was tested by

inoculation of animals and by using such cultures to inoculate other cultures that subsequently developed nuclear inclusions. The cytogenesis of the intranuclear inclusions in tissue cultures involves a disturbance in the nucleoli in cooperation with the margination of the nucleoplasm, which results in a body surrounded by a clear zone, the halo. These stages were observed in coverslip cultures fixed in alcohol solution of mercuric chloride and stained with eosin-hematoxylin. Microscopic observations of tissue cultures showing inclusions failed to reveal indications that the inclusions are motile. Cells containing inclusions continue to multiply until overcome by the virus, which finally destroys them. Examination of the stained coverslip cultures in different stages of growth illustrates this beyond question. The basophilic granules embedded in the inclusions in touch preparations, and the fact that the inclusions become autolyzed in cultures along with other cells, would indicate the protein nature of the inclusion. Moreover, fat stains failed to color the inclusions either in fresh smears of infected testis or in tissue cultures. We failed to infect immune testicular tissue previously soaked in Tyrode's solution for one hour even by exposing such washed tissue to the virus for the same length of time. This is contrary to the results obtained by Andrewes. Tissue cultures of normal rabbit testis when brought in contact with the virus for one hour failed to show inclusions in the presence of immune plasma. This result is in disagreement with that obtained by Andrewes. Since immune plasma inhibits the action of virus III on cultures of normal rabbit testis, and since the immune testicular tissue cannot be infected even after washing with Tyrode's solution, it appears that the immunity resulting from virus III infection is of both cellular and humoral type.

AUTHORS' SUMMARY.

THE INFLUENCE OF DIET ON EXPERIMENTAL COCCIDIOSIS IN CHICKENS. ENA A. ALLEN, Am. J. Hyg. **15**:163, 1932.

Chickens infected with Eimeria tesella were maintained under practically identical conditions except for diet. Some were given diets high in protein and high in vitamins, while others were given diets low in protein and low in vitamins, and the oocyst production was determined. It was found that the oocyst production was lower during the first five days in the chickens on the high diets but that after this time the production was higher.

PAUL MERRELL.

THE LOCALIZATION OF GIARDIA CANIS AS AFFECTED BY DIET. H. TSUCHIYA, Am. J. Hyg. **15**:232, 1932.

This investigation was undertaken with the view of determining the localization of Giardia canis throughout the intestinal tracts of four young puppies experimentally infected with the organisms. The results showed that the duodenum and jejunum were the optimum habitats. Encystment occurred at the level where the bacterial flora commenced to be of complex type. From the distribution of Giardia canis, the intestinal tract may be divided into four apparently distinct zones, differing with respect to the biology of the flagellates present in their respective contents. These may tentatively be designated as the zone of division (the upper part of the duodenum), the zone of optimum localization (the lower part of the duodenum and the entire jejunum), the zone of minimum localization and initial encystment (the ileum) and the zone of encystment (the large intestine, especially the cecum).

FROM THE AUTHOR'S SUMMARY.

INFECTIOUS ORAL PAPILLOMATOSIS OF DOGS. W. A. DEMONBREUN and E. W. GOODPASTURE, Am. J. Path. **8**:43, 1932.

Infectious papillomas occurring in the mouths of dogs are described. The general histologic characteristics of the lesions are very similar to those of human warts. Basophilic intranuclear bodies, similar to the Lipschütz bodies

of human warts, occur in a few of the large wart cells of the older lesions. Their connection with the etiologic agent of the disease remains to be proved. Judged from our experiments practically all puppies are susceptible to the disease, but little is known regarding the proportion of older dogs that are susceptible. The average period of incubation in healthy puppies varies from thirty to thirty-three days, but may be as much as ten days longer in malnourished, sickly puppies. The lesions usually heal spontaneously. Regression in the experimental lesions occurs somewhat earlier than in the natural infection. Puppies that have recovered from the disease are immune to reinfection. We have not succeeded in inducing the disease in rabbits, rats, mice, guinea-pigs, kittens or monkeys. In puppies, the disease is easily transmitted in series by means of Berkefeld filtrates obtained from the lesions. The virus possesses a high degree of cellular specificity, apparently affecting only the mucous membranes of the mouth. The virus may be preserved for long periods in equal parts of glycerol and saline solution, or by drying the infectious tissue in vacuo while frozen. Subjection of the virus to a temperature of 58 C. for one hour renders it noninfectious. A temperature of 45 C. for a similiar period does not appreciably impair its virulence.

AUTHORS' SUMMARY.

VACCINE VIRUS PNEUMONIA IN RABBITS. R. S. MUCKENFUSS, H. A. MCCORDOCK and J. S. HARTER, Am. J. Path. **8**:63, 1932.

A characteristic form of pneumonia can be produced in rabbits by the introduction of vaccine virus into the lungs. The alveoli first contain coagulated albuminous fluid and fibrin, and later a cellular exudate composed principally of large mononuclear cells. Necrosis of the exudate and of the alveolar walls leads to hemorrhage and to the appearance of polymorphonuclear leukocytes. The perivascular lymphatics are distended with coagulated fluid. The walls of many of the larger blood vessels are edematous and often show diffuse infiltration of all the coats by polymorphonuclear leukocytes. Guarrieri bodies have been demonstrated in the epithelial cells of the bronchi in four animals.

AUTHORS' SUMMARY.

HISTOPLASMOSIS (DARLING) WITHOUT SPLENOMEGALY. R. M. CRUMRINE and JOHN F. KESSEL, Am. J. Trop. Med. **11**:435, 1931.

In a case of lymphadenitis, fungi were found in the abdominal lymph nodes, spleen, liver, intestine and lungs. The organisms encountered and the structural changes produced resemble more closely the findings reported in cases of Darling's histoplasmosis than those in any other condition known to the writers. It would thus appear that the present report marks the fifth case of histoplasmosis to be reported to medical science, and the second to be recorded in North America. Two differences between this and previous cases are apparent, however: The spleen was not enlarged at any time, whereas splenomegaly has been a constant characteristic in the other four cases. This case exhibited acute colitis, and had death not resulted so early it is possible that the spleen eventually would have become enlarged. In addition to the small intracellular phase of the organism reported by previous workers, a second or extracellular phase is recorded in which the organism is surrounded by a "halo" or capsule of considerable thickness. Whether this is a true capsule or a reaction product of the tissue is uncertain, but comparison of this structure with the capsules formed by yeastlike stages of other fungi leads to the conclusion that it probably is a mucinoid capsule, produced by the organism itself.

AUTHORS' SUMMARY.

STREPTOCOCCUS VARIANTS. C. D. GALLAGHER, J. Bact. **22**:363, 1931.

Of the eighteen matt strains of Streptococcus hemolyticus carried on infusion agar without blood for from 18 to 170 transplants, only two strains exhibited ability to give rise to glossy variants. One of these strains required 49, the other 75, transplants before showing any glossy colonies. These glossy derivatives, growing with difficulty in the presence of whole, unheated blood and unable to produce as potent a toxin as their matt forms, acquired the ability to change the color of chocolate agar from dark reddish brown to light greenish yellow-brown, a phenomenon not previously described. One of the glossy variants, when grown in 1 per cent normal rabbit serum broth for seven transplants, gave rise to a very rough or pebbly form, which was serologically identical with the glossy form, and which preserved its ability to change the color of the chocolate agar. In the study of daily throat cultures taken over a period of from two to six weeks from five patients with scarlet fever and three with erysipelas, all colonies of S. hemolyticus were of the matt type and no colonies of the glossy or pebbly forms were isolated.

AUTHOR'S SUMMARY.

THE LYSIS OF PNEUMOCOCCUS BY SAPONIN. S. J. KLEIN and F. M. STONE, J. Bact. **22**:387, 1931.

Pneumococci are not dissolved by saponin when tested in plain broth culture. Treatment of the bacteria with cholesterol renders them susceptible to complete and rapid lysis by saponin. The cholesterol exerts a direct action on the bacteria, independent of bacterial reproduction. The bacteria must be in contact with the cholesterol for a definite period of time prior to the addition of saponin in order to obtain lysis. Excess of saponin inhibits the sensitization by cholesterol. Conversely, excess of cholesterol inhibits lysis by saponin. Animal fluids, e. g., blood, or ascitic and pleural fluids, act similarly to cholesterol. Evidence is presented to show that the activity of these fluids is due to their cholesterol content. When cholesterol is esterified, it loses its affinity for saponin, and becomes incapable of sensitizing pneumococci to saponin. The theory is advanced that the lysis is due to a union of saponin with the cholesterol assimilated by the bacteria during sensitization. The parallelism between saponin bacteriolysis and saponin hemolysis is noted.

AUTHORS' SUMMARY.

INFECTIOUS LARYNGOTRACHEITIS OF CHICKENS. J. R. BEACH, J. Exper. Med. **54**:801 and 809, 1931.

The causative agent of infectious laryngotracheitis of chickens was found to be present in bacteriologically sterile tracheal exudate, spleens and livers of diseased fowls. The causative agent was present regularly in the tracheal exudate, in the spleens of about 60 per cent, and in the livers of about 30 per cent of chickens with active infectious laryngotracheitis. Suspensions of the spleen and liver were less effective in inducing the disease than those made from the tracheal exudate. This finding, with absence of pathologic changes in the spleens and livers, would seem to indicate that they are not actively involved, but that the causative agent is carried to them by way of the blood. The disease could, in our experience, be produced only in chickens. Domesticated ducks and several wild and free-flying species of birds, including sparrows, crows, starlings, doves and pigeons, were found to be refractory, and so, too, were rabbits, guinea-pigs, white rats and one pig that was tested.

Experiments have shown that tracheal exudate from two strains of laryngotracheitis of chickens from New Jersey and two from California when suspended in bouillon and passed through Berkefeld V filters will produce the disease. Two of six Berkefeld N filters allowed the etiologic agent to pass, whereas four did not. Attempts to produce the disease with Seitz filtrates were unsuccessful. These results demonstrate that laryngotracheitis is caused by a filtrable virus which because of its size or some other property does not pass readily through the finer

filters. It has been shown that the serums from fowls that have recovered from an infection with one of the New Jersey viruses will neutralize the same strain and also the one California strain tested. In order to demonstrate neutralization conclusively it was necessary to titrate samples of dried virus and in the tests to use approximately ten infecting doses. The virus dried over calcium chloride for ten days and then stored in the refrigerator for sixty days produced disease. Kept over calcium chloride for a month it was still active, and when dried by Swift's method it remained alive for five months.

AUTHOR'S SUMMARIES.

HISTOPATHOLOGY OF INFECTIOUS LARYNGOTRACHEITIS IN CHICKENS. O. SEIFRIED, J. Exper. Med. **54**:817, 1931.

The characteristic lesions of infectious laryngotracheitis are ordinarily restricted to the respiratory tract and are most pronounced in the larynx and trachea. Sometimes the eyelids are affected. A certain percentage of the cases are associated with bronchitis and peribronchitis, and pneumonic areas and hemorrhages in the lung, while involvement of the nasal passages, communicating sinuses and eyes seems to be dependent on the mode of infection and the course of the disease. The virus affects the epithelial cells primarily, but soon inflammation develops in the submucosa and underlying parts. Edema is often extremely pronounced in the submucosa. The destruction taking place at later stages is due to edema, cellular infiltration and hemorrhages, and in some instances to secondarily invading bacteria. Characteristic intranuclear inclusions in the epithelial cells of the trachea are present in many cases. They bear a close resemblance to the inclusions occurring in herpes, varicella, virus III of rabbits and submaxillary gland disease of guinea-pigs.

AUTHOR'S SUMMARY.

THE DERMAL PNEUMOCOCCIC LESION IN THE RABBIT. K. GOODNER, J. Exper. Med. **54**:847, 1931.

An attempt has been made to analyze the factors involved in the development and localization of the dermal pneumococcic lesion in the rabbit. The character and quantity of the edema fluid that forms during the early phases of the lesion are intimately concerned in its development and spread. The fluid contains an antithrombic substance, probably derived from the pneumococci, and delayed coagulation probably facilitates its movement through the tissue. The direction of spread in the skin is determined by gravity, and the fluid finally localizes in the more dependent regions. The distance that the pneumococcic lesion travels and the characteristics of the local tissue have much to do with the amount of fluid that accumulates. Studies are also reported of some factors that alter the rate of spread of the edema fluid. An acceleration in rate occurs when Bacillus influenzae is used as an associative infective agent with the pneumococcus.

AUTHOR'S SUMMARY.

THE HISTOLOGIC CHANGES AND THE FATE OF LIVING TUBERCLE BACILLI IN TUBERCULOUS RABBITS. M. B. LURIE, J. Exper. Med. **55**:31, 1932.

The mononuclears of the liver, splenic pulp and bone marrow destroy tubercle bacilli more readily than those of the lung, kidney or splenic corpuscle. The multiplication of tubercle bacilli in an organ and their accumulation within mononuclears are accompanied by active new formation of these cells by mitosis. When these mononuclears are transformed into mature epithelioid cells and when tubercles have reached their maximum development, the bacilli have undergone extensive destruction and are disappearing. Tubercle bacilli of moderate virulence (human type and B C G) are usually effectively destroyed within epithelioid cells of all organs. In the lung and kidneys, bovine bacilli persist within epithelioid cells, but in other organs they are usually destroyed. Tubercle bacilli are less effectively destroyed within epithelioid cells collected in the alveoli of the lung than in those

forming tubercles in the interstitial tissues. After multiplication of tubercle bacilli has ceased, regeneration of mononuclears by mitosis becomes less active, and now Langhans' giant cells may be formed from preexisting epithelioid cells. Lymphocytes and encapsulation of tubercles by granulation tissue do not cause destruction of tubercle bacilli. Immediately after infection, accumulation of the less virulent types of tubercle bacilli in the tissues does not cause caseation, and the more virulent bovine bacilli produce this change only in the lung. Later, caseation occurs in the presence of a small number of bacilli, and must be thought of as due, in part at least, to sensitization.

AUTHOR'S SUMMARY.

THE TRANSFORMATION OF R PNEUMOCOCCI INTO S FORMS BY THE USE OF PNEUMOCOCCUS EXTRACTS. J. L. ALLOWAY, J. Exper. Med. **55**:91, 1932.

Avirulent R pneumococci derived from S forms of a specific type may be changed by growth in broth containing anti-R serum and a heated, filtered extract of S pneumococci of a different type into virulent S organisms identical in type with the bacteria extracted. This has been accomplished in the case of R strains derived from pneumococci of type II, with extracts prepared from S forms of types III and I. The constituents of the extracts supply an activating stimulus of a specific nature in that the R pneumococci acquire the capacity of elaborating the capsular material peculiar to the organisms extracted.

AUTHOR'S SUMMARY.

THE ACCUMULATION OF IRON IN TUBERCULOUS AREAS. V. MENKIN, J. Exper. Med. **55**:101, 1932.

Repeated intravenous injections of ferric chloride are followed by an increase in the survival time of tuberculous rabbits. In the particular series of experiments reported, this increase amounted to about 78 per cent over the average survival time of control rabbits. Tuberculous animals given repeated injections of ferric chloride increased in weight during part of the period of these injections. The level reached markedly exceeded that attained by control rabbits. Both control and experimental animals died of generalized tuberculosis. At the time of death there was no indication of any differences in degree of pathologic involvement between the two groups of animals.

AUTHOR'S SUMMARY.

MULTIPLICATION OF THE VIRUS OF MEXICAN TYPHUS FEVER IN FLEAS. H. MOOSER and M. R. CASTANEDA, J. Exper. Med. **55**:307, 1932.

The virus of Mexican typhus fever has been shown to multiply abundantly in the following species of fleas: Xenopsylla cheopis, Ceratophyllus fasciatus, Leptopsylla musculi, Ctenocephalus canis, Ctenocephalus felis. In all fleas, Rickettsia prowazeki was demonstrated within the epithelial cells of the stomach and within the malpighian tubules. Whereas in infected lice enormous numbers of these organisms are discharged from the disintegrating cells into the intestinal content, only few rickettsiae are found in the lumina of the fleas' intestines. They are held back by the peritrophic membrane, which covers the mucosa of the entire stomach. Rickettsiae seem to enter the lumen of the intestine almost exclusively by the route of the malpighian tubules. Observations were made that seem to indicate that the fleas recover from the infection, and that they are able to regenerate the partly destroyed intestinal mucosa. An explanation is given for the relative harmlessness of fleas as vectors of typhus.

AUTHORS' SUMMARY.

EPIDEMIC DISEASES AMONG WILD ANIMALS. CHARLES ELTON, J. Hyg. **31**:435, 1931.

Outbreaks of epidemic disease are common in populations of wild animals, including species little influenced by contact with the diseases of human beings or domestic animals. Such epidemics form one of the commonest factors responsible for fluctuations in numbers of wild mammals. An attempt is made to summarize the available published records of such epidemics, while certain unpublished records are contained in an appendix. Little is known of the causes of these epidemics except in the cases of plague and tularemia. The fluctuations in numbers of some wild mammal populations are sufficiently regular to make the forecasting of epidemics possible. This method is already applicable to wild mice. Mouse periodicities are discussed in detail, with special reference to epidemics and their causes. Development of the methods of forecasting epidemics will make possible the prediction of epidemics among many other wild mammals, and render intensive pathologic and epidemiologic studies more practicable than they have hitherto been.

AUTHOR'S SUMMARY.

THE EFFECT OF CONCENTRATION AND OF VARIOUS TISSUE CONSTITUENTS ON THE VIRULENCE OF THE POLIOMYELITIS VIRUS. CLAUS W. JUNGEBLUT, J. Immunol. **22**:99, 1932.

Titration of poliomyelitic virus cord suspensions of varying percentages shows that there is a particular concentration with maximum virulence, below which the dilutions become progressively less infective, and above which virulence is likewise diminished. Berkefeld filtrates of virus cord suspensions are at times more virulent than corresponding unfiltered suspensions, although exceptions occur. Neither normal monkey cord nor normal monkey brain, when added in vitro to virus filtrates, has any appreciable effect on the virulence of the virus. The results with convalescent cord are too irregular to indicate clearly the presence of a neutralizing principle in the immune tissue. Normal monkey testicle added to virus filtrates in vitro frequently produces a conspicuous diminution of virulence of the virus in the supernatant fluid. The extent of this antagonistic effect varies with different monkey testicles. Normal rabbit testicle, under similar conditions, seems slightly to enhance the virulence of the virus.

AUTHOR'S SUMMARY.

MICROBIC DISSOCIATION IN THE BRUCELLA GROUP. M. S. MARSHALL and DOROTHY JARED, J. Infect. Dis. **49**:318, 1931.

By means of prolonged cultivation on agar containing specific antiserum and repeated selection, R types of most strains of Brucella are obtained. The R forms are relatively stable, and the S→R change appears to be continuous. Metabolic differences between S and R types are not clear. S types of various origins in guinea-pigs regularly produced pathologic changes, low agglutination titers and positive cultures. The corresponding R types induced few signs of infection. In three rabbits a hypopyon was produced by S cultures but not by R cultures.

EDNA DELVES.

CULTURES OF TREPONEMA MICRODENTIUM. E. E. ECKER and L. A. WEED, J. Infect. Dis. **49**:355, 1931.

Contaminated cultures of T. microdentium were purified by centrifugation. Transfer of the surface layers of the centrifugated cultures to gelatinized human serum containing livers of guinea-pigs yielded pure strains.

AUTHORS' SUMMARY.

ISOLATION OF THE SPIROCHETE OF RAT-BITE FEVER FROM THE SALIVA OF RATS. L. BORBI, Pathologica **23**:120, 1931.

The saliva of rats contains a spirochetal form that is pathogenic for the guinea-pig and that is probably identical with the causal agent of rat-bite fever in man. The spirochetes of rat-bite fever and of spontaneous spirochetosis of rats are identical. Experimental infection is readily produced in guinea-pigs.

E. HAAM.

THE GROWTH OF BACTERIA IN DEAD TISSUES. G. TRUFFI, Pathologica **23**:205, 1931.

Dead tissues, even of immune animals, not only lose the antagonistic power of the development of the anthrax bacillus, but become, without the addition of any other nutritional material, a very favorable medium for the growth of the bacillus.

E. HAAM.

INGUINAL LYMPHOGRANULOMA. A. COHN and L. KLEEBERG, Dermat. Wchnschr. **92**:580, 1931.

Intracerebral injections of 0.1 cc. of an emulsion of pus diluted 1:5 from a lymphogranulomatous lymph node were made in a Cynomolgus monkey. The animal died in sixteen days, after the appearance of disturbances in equilibrium, somnolence and refusal to eat. The hyperemic meninges were cut up fine, mixed with a few cubic centimeters of physiologic solution of sodium chloride and, together with the cerebrospinal fluid, sterilized at 60 C. for one and one-half hours on two successive days. A skin test, performed after the method of Frei, was made on five patients with inguinal lymphogranuloma and on five healthy controls, 0.1 cc. of the emulsion consisting of cerebrospinal fluid and meninges. A positive reaction in the form of a papule with an erythematous margin developed in the five patients, but not in the controls. It is concluded that the virus causing a cutaneous reaction in patients with inguinal lymphogranuloma is transmissible to monkeys, and that it is not inactivated for the cutaneous reaction by heating for three hours at 60 C.

LAWRENCE PARSONS.

AGRANULOCYTOSIS AND MYELOGENOUS LEUKEMIA IN TWO SISTERS INFECTED WITH THE SAME MICRO-ORGANISM. ERNST WOLFF, Folia haemat. **44**:38, 1931.

Two sisters died, one with signs typical of agranulocytosis, the other with those characteristic of aleukemic myelo-adenosis. The fact that in both instances Streptococcus hemolyticus was present in the blood and in the tissues led the author to the conclusion that agranulocytosis is not a disease *sui generis*, but is a reaction to sepsis. He quotes other writers who are of the same opinion.

B. M. FRIED.

THE TRANSMISSION OF INGUINAL LYMPHOGRANULOMA TO GUINEA-PIGS. K. MEYER, H. ROSENFELD and H. E. ANDERS, Klin.Wchnschr. **10**:1653, 1931.

The subcutaneous injection of exudate or crushed lymph gland tissues of patients with inguinal lymphogranuloma into guinea-pigs transmits the disease. Inoculations in ten cases were successful. The disease was transmitted from one guinea-pig to another, and in this way one virus strain was transplanted to the fifth, and another to the twelfth, generation. The virus passes through the Berkefeld filter and is markedly resistant to heat and the action of glycerin. The specific agent transmitted to the guinea-pig is not localized at the site inoculated but

spreads by way of the lymph channels and the blood. Systemic lesions occur in the liver and lungs. The diseased lymph nodes of the guinea-pigs are histologically the same as those of man.

AUTHORS' SUMMARY.

THE TRANSMISSION OF INGUINAL LYMPHOGRANULOMA TO RABBITS AND GUINEA-PIGS. H. FREUND and F. REISS, Klin. Wchnschr. **10**:1658, 1931.

In rabbits infected by the subdural inoculation of material from cases of inguinal lymphogranuloma, a characteristic meningeal encephalitis developed. Enlargement of the lymph nodes of the groins of rabbits was produced with material from man as well as with brain tissues from specificially diseased animals. These lymph glands had the characteristic histologic changes. Similar transmission experiments were successful in guinea-pigs. The infection can be transmitted from one animal species to another by inoculation.

ENDOCARDITIS DUE TO BACILLUS INFLUENZAE. H. FRANK, München. med. Wchnschr. **78**:1509, 1931.

The author reports chronic endocarditis caused by B. influenzae. His review discloses that in the twenty-one cases reported, none of the patients lived and only one became free from bacteria. The endocarditis caused by B. influenzae corresponds clinically to the endocarditis produced by Streptococcus viridans.

THE EFFECT OF HUMAN TUBERCLE BACILLI ON PIGEONS. M. A. KUSCHNARJEW, Virchows Arch. f. path. Anat. **276**:95, 1930.

The inoculation of human tubercle bacilli into pigeons resulted in the formation of a nonspecific granulation tissue in all the organs. The bacilli could be recultivated from the blood and organs of the infected pigeons, but guinea-pigs given injections of an emulsion of the organs remained healthy.

W. SAPHIR.

THE NATURE OF THE BACTERIOPHAGE. ERNST FRANKEL, Ztschr. f. Immuniätsforsch. u. exper. Therap. **71**:278, 1931.

Two bacteriophages (Flexner and Colon) were highly concentrated by adsorption with aluminum hydroxide and subsequent washing out with phosphate solutions. An attempt to achieve the same by centrifugating at a very high speed was not successful.

I. DAVIDSOHN.

RABIES VIRUS IN HUMAN SALIVA. H. PALAWANDOW and A. I. SEREBRENNAJA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **71**:350, 1931.

From a study of five cases it appears that the saliva of patients affected with rabies contains the virus, and that from 2 to 3 cc. of it is necessary for intramuscular injection, preferably into guinea-pigs, which ought to be kept in a cool place and on a meager diet.

I. DAVIDSOHN.

THE OCCURRENCE OF UNDULANT FEVER IN SWEDEN. GUNNAR OLIN, Ztschr. f. Immunitätsforsch. u. exper. Therap. **71**:531, 1931.

The first case of undulant fever in Sweden was diagnosed in 1927. Since then about 100 cases have been reported annually. The infection is prevalent in cattle. An agglutinin titer up to 1:80 was found in the blood of persons living in an isolated section of Sweden, where the infection does not occur in cattle; such a titer was therefore set as the limit for nonspecific agglutinins. In a large number of serums, specific agglutinins were found in 0.56 per cent and complement-fixing antibodies in a similar number. They were all from persons who had never had symptoms or a history of undulant fever and who apparently went

through a latent infection. This explains why the disease is relatively more prevalent among the urban population; the immunity among the rural population is greater. Children are, as a rule, not affected. Women are affected twice as frequently as men.

I. DAVIDSOHN.

THE INFLUENCE OF THE BACTERIOPHAGE ON THE HEMOLYTIC ACTION OF TYPHOID BACILLI (PHENOMENON OF FRIEDBERGER-VALLEN). L. BIANCHI and C. CALLERIO, Ztschr. f. Immunitätsforsch. u. exper. Therap. **72**:155, 1931.

About 80 per cent of the strains of typhoid bacilli used produced slight hemolysis of the red blood cells of sheep, but not those of man or of rabbits. The addition of bacteriophage made nonhemolytic or only slightly hemolytic strains acquire marked hemolytic properties. In some cases bacteriophage was demonstrated in the cultures of spontaneously hemolytic strains.

I. DAVIDSOHN.

Immunology

ANTISERUM IN EXPERIMENTAL POLIOMYELITIS. B. F. HOWITT, J. Infect. Dis. **50**:26, 47, 1932.

The prolonged immunization of two goats and a sheep with poliomyelitic virus over a period of years resulted in the development of antiviral substances that were capable in a certain number of instances, of protecting monkeys against infection, both when the substances were tested by the different methods of in vitro neutralization and when used therapeutically or prophylactically.

In monkeys in the preparalytic stage the percentage of recovery from experimental poliomyelitis was greater when serum from convalescent monkeys was given intramuscularly than when it was administered by the combined intrathecal and intravenous method. Paralysis, however, was rarely prevented, and with one exception recovery was accompanied by varying degrees of atrophy of the affected muscles. One hundred per cent mortality occurred if treatment was given after the onset of paralysis, while repeated injections of serum seemed no more effective than a single dose.

AUTHOR'S CONCLUSIONS.

ANTIBODY RESPONSE TO TYPHOID VACCINE. L. TUFT, E. M. YAGLE and S. ROGERS, J. Infect. Dis. **50**:98, 1932.

Comparison of the titers of agglutinins and of complement-fixing antibodies after intradermal, subcutaneous, intramuscular, intravenous and oral methods of administration of mixed typhoid vaccine reveals a uniformly better and more persistent response after local injection, particularly after intradermal injection. Such results may be explained on the basis of local stimulation of the formation of antibodies by the reticulo-endothelial cells, which are particularly abundant in the skin and subcutaneous tissues, or possibly by a slow absorption of the antigen. The antibody response after any of the methods showed definite dependence on the antigenic potency or the age of the vaccine — the older the vaccine, the less the response. The general observations of others as to time of appearance of the agglutinins and complement-fixing antibodies, the variability in titer and the tendency to early disappearance were corroborated in our studies. A complete lack of uniformity in the titers of agglutinins and complement-fixing antibodies was observed with many serums; an adequate explanation for this is not apparent. The antibody response after oral administration of the vaccine was completely negative, in spite of different strains of vaccine and different groups of persons. From a therapeutic standpoint, the intradermal injection of small doses of a freshly prepared and antigenically potent mixed typhoid vaccine receives experimental justification and has in our hands proved satisfactory.

AUTHORS' SUMMARY.

THE FLOCCULATION REACTION WITH STAPHYLOCOCCAL TOXIN. F. M. BURNET, J. Path. & Bact. **34**:759, 1931.

A true toxin-antitoxin flocculation can be obtained with staphylococcal toxin and antitoxin. The point of optimal flocculation is constantly related to the neutral point as judged by hemolytic titrations, but is always in the zone of antitoxin excess, usually corresponding to a mixture of about 0.6 equivalent of toxin to 1 of antitoxin. The supernatant fluid from flocculation tests made with optimal proportions of toxin and antitoxin always contains free antitoxin. The washed toxin-antitoxin floccules are soluble in acetate solution at p_H 3.3. From such a solution either toxin or antitoxin can be recovered by suitable methods. Carefully prepared anatoxin shows flocculations unaltered from those of the original toxin. The binding power of anatoxin under the conditions of the flocculation test is equal to that of the toxin of origin in contrast to the behavior in dilute solution, where it is half that of the toxin. Staphylococcal toxin is relatively highly resistant to heat. The effects of heating to 100 C. on hemolytic titer, binding power and flocculating power are described and compared.

AUTHOR'S SUMMARY.

ACTION OF ANTIVACCINIAL SERUM ON VACCINIA VIRUS. R. W. FAIRBROTHER, J. Path. & Bact. **35**:35, 1932.

Contact in vitro between immune serum and vaccinia virus plays an important rôle in determining the infectivity of the mixture on intracerebral inoculation. This is in marked contrast with the results obtained by intradermal inoculation.

AUTHOR'S SUMMARY.

SALMONELLA AGGLUTINATION AND RELATED PHENOMENA. P. B. WHITE. J. Path. & Bact. **35**:77, 1932.

In addition to the carbohydrate haptens characterizing the S and R forms of Salmonella, an alcohol-soluble protein, here termed Q, is concerned in the somatic serology of these organisms. Q is readily extracted by warm 95 to 97 per cent alcohol in the presence of hydrochloric acid. Q is a full antigen and stimulates the development of potent precipitating antibodies. Q occurs in all the serologic types and variant forms of Salmonella, and up to the present no evidence of interspecific or intervarietal differences has been obtained. Besides the ordinary S and R forms of Salmonella there exist rough races, derived from strains long cultured in the laboratory, which lack the S and R carbohydrate haptens, and in which no corresponding constituent has yet been demonstrated. These races, here named -forms, differ in agglutinative properties from ordinary R forms. S. forms do not appreciably agglutinate with anti-Q serums, though Q is certainly a constituent of the smooth surface. With anti-Q serums the -forms (and intermediate R forms) agglutinate much more vigorously than do ordinary R forms, which are very slowly clumped. Q fractions from coliform, dysentery and proteus bacilli have proved serologically similar to those obtained from salmonella bacilli, but no cross-reaction has been obtained with anti Q (salmonella) serums and material extracted from staphylococci and tubercle bacilli. The process of extracting Q, though it does not damage or interfere with the essential reactions of the carbohydrate haptens, causes a severe reduction, or almost complete loss, of somatic agglutinability. It is possible that this loss of somatic agglutinability is actually due to the removal of Q from the surface of the bacilli, in that this substance is precipitable by physiologic salt solution and has to a marked degree the power of clumping and carrying down bacteria in suspension; attempts to return lost agglutinability by adding Q to mixtures of antiserum and desensitized bacilli have been in part successful. An attempt is made to formulate a theory of somatic agglutination on this basis.

AUTHOR'S SUMMARY.

FRACTIONATION OF TYPHOID-IMMUNE RABBIT SERUMS. M. L. AHUJA, Indian J. M. Research **19**:601, 1931.

The euglobulin fraction of typhoid-immune rabbit serum is responsible for the floccular H and the granular O types of agglutination. The albumin and pseudoglobulin fractions are devoid of H and O agglutinins. The effect of inactivation for twenty minutes at 55 C. and aging at room temperature for from forty-eight to ninety-six hours was studied on the agglutination titer of twelve typhoid-convalescent human serums and three typhoid-immune rabbit serums. No marked difference in O and H agglutination titers was observed in either series.

AUTHOR'S SUMMARY.

AGGLUTINATION IN LEISHMANIASIS. R. ROW, Indian J. M. Research **19**:641, 1931.

The agglutination is a group reaction, and agglutinins are definitely demonstrable in all cases of kala-azar, in some more than in others. The agglutinins are usually not found in cutaneous leishmaniasis. The antibodies are most easily formed in the rabbit by injections of the products of Leishmania. The agglutination test is of scientific interest, but will not replace other tests for the clinical diagnosis of leishmaniasis, and is of no value in the differential diagnosis of the several members of Leishmania.

EDNA DELVES.

SERUM PROPHYLAXIS AND TREATMENT IN TETANUS. S. MUTERMILCH and E. SALAMON, Ann Inst. Pasteur **47**:277, 1931.

Intraspinal administration of tetanus antitoxin was much more effective than subcutaneous injection in protecting rabbits against toxin inoculated intramuscularly. This was true whether the serum was given before or after the toxin.

Neither toxin nor antitoxin could be demonstrated in the peripheral nerves of rabbits after intraspinal injection. Antitoxin inoculated into the brain was fixed by cerebral tissue and was not completely eliminated until after six days. Hence, it is believed that neutralization takes place in intimate contact with the central nervous system rather than in the peripheral nerves or in the cerebrospinal fluid when the serum is injected intrathecally. Rabbits responded more readily to vaccination with anatoxin when given intraspinally.

It is recommended that human tetanus be treated with a mixture of antitoxin and anatoxin injected intraspinally under chloroform anesthesia.

J. B. GUNNISON.

Tumors

THE VITAL STAINING OF RABBIT CARCINOMA. R. C. TILGHMAN and F. C. LEE, Bull. Johns Hopkins Hosp. **49**:360, 1931.

In the first series of animals, trypan blue alone was injected, and it was found that the dye lodged primarily in the phagocytic wandering mononuclear cells, which were situated in great numbers in the stroma surrounding the tumor nodules. To a much less extent were these cells found within the nodules. Only occasionally did the cancer cells take up the dye, and in such instances the cells were situated near the periphery of the nodule. In the second series of animals, a course of trypan blue was given first, followed by a similar series of injections of carmine. By the use of these two contrasting dyes it was seen that the oldest areas of carcinomas stained predominantly blue and the youngest red, while a mixture of these two colors was seen in the regions of intermediate growth. The dye was in the phagocytic cells; some cells contained only the blue and others only the red, but the majority contained both dyes; never were cells seen in which a vacuole contained particles of each dye. The fact that some of these cells had

only the blue dye showed that they were incapable of taking up the red. In this respect, an instance is afforded in which a "blockade" of certain cells of the reticulo-endothelial system occurred, and an exception is thus furnished to the general belief that such cells cannot be blocked. The tremendous number of these cells, particularly in contrast to the relatively few lymphocytes, indicated a peculiar significance for them in cancer growth. Furthermore, their distribution in the area of cancer suggested that their ability to move about in the tissues had been exaggerated. Again, the young, or red-stained, phagocytic cells are always present at the areas of cancer necrosis, even if the surrounding tissue was composed of relatively old cancer cells as judged by the predominantly blue color of the macrophages. Whether present in the cancer cell itself or in the monocyte, apparently the dyes did not give any indication of retarding cancer growth.

AUTHORS' SUMMARY.

INCIDENCE OF CANCER IN TARRED AND SHELTERED MICE. P. ROUS and E BOTSFORD, J. Exper. Med. **55**:247, 1932.

Mice sheltered for long periods from the intercurrent access of living entities out of the environment developed tar cancer with the same frequency as controls exposed to an unusual extent. This happened although the food of the two groups differed profoundly in character.

AUTHORS' SUMMARY.

NUTRITIONAL REQUIREMENTS IN VITRO OF NORMAL AND MALIGNANT MOUSE EPITHELIUMS. L. SANTESSON, J. Exper. Med. **55**:281, 1932.

The cultivation in vitro of mouse tissues derived from normal organs, from eighty-six spontaneous epithelial tumors of the mammary gland, and from twenty-seven Ehrlich carcinomas has been undertaken, together with a study of the properties of the various cell types. The tissues liquefied fibrin from mouse and rat plasma more readily than fibrin from chicken plasma. Clots made of chicken plasma alone, if thoroughly washed, did not inhibit the migration of the cells. Normal and tumor tissues liquefied fibrin from the mouse, rat and chicken more actively than Ehrlich carcinoma did. Mouse epitheliums, both normal and malignant, showed greater activity than connective tissue cells from the same origin and were not overgrown by the latter. Mouse epithelium was more active in rat serum than in mouse or chicken serum, and, in embryonic juice from chickens, mice and rats. None of these fluids, however, supported cell proliferation indefinitely, except in the case of the Ehrlich carcinoma. These results indicate that mouse tissues possess nutritional requirements that are different from those of fibroblasts and epithelial cells of other animals. Nutritive mediums that suffice for prolonged cultivation of the normal and malignant tissues of the rat and the fowl, and also of the Ehrlich carcinoma, are not suitable for the cultivation of adult mouse epithelium derived from normal organs or from spontaneous tumors of the mammary gland. Rat serum supported the life of spontaneous tumors for a limited period of time only, whereas it enabled the Ehrlich carcinoma to proliferate indefinitely. Cells of normal organs and spontaneous tumors were not capable of invading normal tissues as Ehrlich carcinoma did.

AUTHOR'S CONCLUSIONS.

BRONCHOGENIC CARCINOMA. F. R. MENNE, M. BISAILLON and T. D. ROBERTSON, Northwest Med. **30**:155, 1931.

A study of sixteen cases of primary bronchogenic carcinoma with correlation of the pathologic and clinical findings is presented. Primary bronchogenic carcinomas are divisible into two distinctive groups, the hilar nodular and the diffuse necrotic. Further pathologic classification is superfluous and unnecessary. It is pointed out that the cell type does not offer an exact means of differentiating the various forms. The initial site may be found in any part of the bronchial lining

or the submucous glands, but is most frequent in the primary and secondary bronchi. Primary bronchogenic carcinoma probably never arises from the atrial lining cells. The symptoms, physical signs and roentgenologic findings can all be explained on the basis of the pathologic changes. In our opinion there is a definite increase in the incidence of primary bronchogenic carcinoma.

AUTHORS' SUMMARY.

ADSORPTION EXPERIMENTS WITH THE VIRUS OF ROUS SARCOMA. ANTOINETTE PIRIE, Brit. J. Exper. Path. **12**:373, 1931.

The adsorption of the virus of Rous sarcoma onto, and the elution of it from, alumina and kaolin is described. Such elutes are inactivated during incubation as rapidly as the crude filtrates, and are preserved by cyanic acid in the same way. The nitrogen of the infective dose of the elutes is of the order of 10^{-3} mg.

AUTHOR'S SUMMARY.

EXPERIMENTS ON THE PRODUCTION OF TUMOURS ON THE SOMATIC MUTATION HYPOTHESIS. J. C. MOTTRAM, Brit. J. Exper. Path. **12**:378, 1931.

A sarcoma-like tumor appeared in a rat at the site of inoculation of a testicular emulsion which had been exposed to radiation in vitro. This was the only tumor arising in many experiments of a similar kind.

AUTHOR'S SUMMARY.

AN APPARATUS FOR THE PREPARATION UNDER STANDARD CONDITIONS OF A HIGHLY POTENT CARCINOGENIC AGENT IN MICE OF LOW TOXICITY. A. F. WATSON, Brit. J. Exper. Path. **12**:441, 1931.

An apparatus originally described by Hague and Wheeler (1929) for their work on the pyrolysis of the paraffins has been adapted for the preparation from purified turpentine of a carcinogenic agent under standard conditions of temperature, etc. The pyrolysis of purified turpentine in this apparatus at 850 C. yields a tar that, after steam distillation, exhibits high carcinogenicity combined with low toxicity when tested on mice. Charts showing the relative effectiveness of the tar prepared in this apparatus, which is simple in type and control, compared with two coal gas tars, are included.

AUTHOR'S SUMMARY.

Society Transactions

NEW YORK PATHOLOGICAL SOCIETY

Regular Meeting, Feb. 25, 1932

PAUL KLEMPERER, *President, in the Chair*

SUBACUTE BACTERIAL ENDOCARDITIS SUPERIMPOSED ON RHEUMATIC AORTIC VALVULAR DISEASE WITH NO PREVIOUS INVOLVEMENT OF THE MITRAL VALVE. IRVIN GRAEF and CLARENCE DE LA CHAPELLE.

A white youth, 18 years of age, came to necropsy from the Third (New York University) Medical Division of Bellevue Hospital. The outstanding features of the past history were four attacks of rheumatic polyarthritis at 8, 14, 15 and 17 years, and frequent attacks of tonsillitis. Clinically, the picture presented was typical of subacute bacterial endocarditis superimposed on an old rheumatic condition of the heart.

At necropsy, the contour of the body and the distribution of the hair were those of a female. The skin was delicate in texture and practically hairless, there being a slight growth in the axillae and over the pubes. In the conjunctiva of the left eye there was a small petechial hemorrhage. There was moderate edema of the lower extremities. Clubbing of the fingers was present. A few grayish-pink remnants of the thymus were found scattered through the fatty tissue in the upper and anterior part of the mediastinum. Bilateral hydrothorax was present, as well as confluent lobular pneumonia of the right upper lobe.

The pericardial sac contained about 500 cc. of clear, yellowish fluid. At the site of the mouth of the coronary sinus there was a small network of fine endothelial bands, in the meshes of which was found a small, grayish-red, firmly attached thrombus. The left auricle was small. The posterior leaflet of the mitral valve showed a few small verrucous vegetations along the line of closure. The aortic leaflet was the seat of two large vegetations, one of which had ulcerated through the substance of the leaflet, causing a fenestration about 4 mm. in diameter. The valve substance elsewhere was slightly thickened, but no blood vessels were seen. The chordae tendineae of this leaflet were slightly thickened, and vegetations had grown down on their surface. The posterior leaflet of the mitral valve was thin, transparent and not vascularized. Its chordae were thin, delicate and not fused or shortened. The left ventricle was hypertrophied and dilated. The aortic valve was stenotic and insufficient. The commissures of all the cusps were firmly fused and adherent. The right anterior cusp showed a triangular-shaped vegetation on the ventricular surface, which was about 8 mm. in length and 4 mm. in width. It was yellowish white and soft. The left anterior cusp had two irregular vegetations on its ventricular surface, which were similar to the other vegetations. The posterior cusp showed no vegetations. The edges of all the cusps of the aortic valve were rolled, thickened and shortened, and the sinuses of Valsalva were diminished in size. The posterior side of the aortic leaflet of the mitral valve was the seat of a series of eccentrically shaped vegetations running in a line from the left anterior cusp of the aortic valve and extending below the free edge of the mitral valve. The aorta was diminished in caliber. The tricuspid and pulmonary valves were normal.

The liver was enlarged and of "nutmeg" appearance.

The spleen was markedly increased in size. A large light-pink infarct was present in the upper pole. The organ was firm and dark red.

The kidneys presented a few petechial hemorrhages. They were congested. The capsule stripped easily, leaving a smooth surface with many petechial hemorrhages.

Lantern slides were shown of sections through the aortic valve and the posterior leaflet of the mitral valve to illustrate the severe involvement of the former and the normal architecture of the latter.

DISCUSSION

C. DE LA CHAPELLE: We thought it important to present this case because of the infrequency of involvement of the aortic valve in rheumatic carditis without concomitant changes in the mitral valve. Emphasis has always been placed on the frequency of involvement of the mitral valve, and rightly so. In a series of ninety-seven necropsies of cases with rheumatic valvular disease analyzed by Coombs, the mitral valve was injured in every case. As a result of this, Coombs concluded that in *all* cases of rheumatic carditis the mitral valve is injured. In Thayer's series of sixty-five consecutive examples of fatal rheumatism with acute endocarditis there was a frequency of 92 per cent. This figure related only to acute changes. However, when he included the cases in which there were evidences of preceding attacks, the mitral valve was affected universally. Hence, we thought it worth while to present a case of this nature and to add one more instance to the group of cases of rheumatic carditis without involvement of the mitral valve.

AN INSTANCE OF METASTATIC CALCIFICATION. DOMINIC A. DESANTO.

By metastatic calcification is meant a condition in which calcium is mobilized from the reservoirs in the bones and is deposited in other tissues of the body. The term was originally employed by Virchow. Wells reviewed the subject and found twenty-nine cases reported in the German literature, to which he added one of his own. The condition occurred in osteomyelitis, in primary and secondary tumors of bone and in leukemias. Well's own cases occurred in a young adult with myelogenous leukemia.

The calcium is most often deposited in the wall of the left auricle, in the pulmonary vessels, in the renal tubules and in the gastric mucosa near the fundus. At all of these sites, Wells pointed out, there is a change in the acidity of the tissue fluids in an alkaline direction, because at these sites acids are excreted (carbon dioxide and hydrochloric acid). The calcium is usually deposited in elastic tissues. These need not be previously injured, and this distinction between metastatic and pathologic calcification is important.

At Bellevue Hospital an example of metastatic calcification was encountered in a 19 year old girl whose history indicated that she had had chronic myelogenous leukemia for about two years. Post mortem, the wall of the left auricle was diffusely calcified. The pulmonary veins were calcified, and when the lung was sectioned, it imparted a grating sensation to the knife. The aorta and the visceral arteries were thrown into calcific ridges, giving the vessels a serrated appearance. Other findings were characteristic of myelogenous leukemia.

Microscopically, calcium was found deposited in the intima of the left auricle, which also showed leukemic infiltration. Calcium was present in the elastic tissue of the alveolar septums and in the intima of the pulmonary veins. Virtually every one of these vessels was affected. Calcium was also deposited in the renal tubules and throughout the aorta and visceral arteries, where it was present selectively in the inner elastic lamina.

DISCUSSION

MAURICE N. RICHTER: Were there any changes in the bones in this case?

DOMINIC A. DESANTO: Unfortunately, we were not permitted to examine the long bones. We took pieces of ilium for examination. We could not find any evidence of decalcification in any one of the bones. The bone marrow, of course, showed the usual leukemic changes. When this condition has been described, it has usually been attributed to a decalcification of the bones as a result of metastatic carcinoma or primary sarcoma of the bone with mobilization of the calcium and secondary deposition at those sites that are, by their physical nature, predisposed to act as sites of deposition of calcium, namely the elastic tissues.

ALFRED PLAUT: What was the condition of the renal papillae—the tips of the pyramids?

DOMINIC A. DESANTO: I have not studied those particular sites. Grossly, I could find no evidence of calcification there. Microscopically, I did not focus my attention on that particular point.

PAUL KLEMPERER: Did the patient have radiotherapy?

DOMINIC A. DESANTO: The patient received radiotherapy two days before death. The period was so short that it would seem it could have had no effect on this pathologic condition, but it was immediately following the roentgen therapy that this peculiar sudden rise in the leukocyte count was observed. The patient had a count of 66,000, with a sudden rise to 1,200,000 two days after roentgen therapy. She had been treated with sodium cacodylate prior to that.

UNIVERSAL POLYPOSIS OF THE COLON, WITH CARCINOMATOUS TRANSFORMATION. L. LICHTENSTEIN.

Of the three cases presented, the first is represented by a specimen taken at autopsy from a man aged 60; it shows innumerable pedunculated, long-stalked polypi of the ascending and transverse colon, giving rise to five distinct primary carcinomas. The other two cases are represented by surgical specimens: one, from a man of 38 years, showing multiple papillomas of the descending colon with malignant degeneration in both the sigmoid and the rectum; the other, from a woman aged 51, shows diffuse polyposis of the ascending colon, with carcinomatous transformation of two polyps. Cases of polyposis adenomatosa diffusa, which appear to have a constitutional basis, often a familial incidence, are few in number, and are to be distinguished from the commonly encountered instances of isolated polyposis of the colon. Oberndorfer (cited by Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926) encountered a single case in a series of over ten thousand autopsies. Stämmler-Schöttler (cited by Henke and Lubarsch) were able to collect from the literature (1923) approximately one hundred cases.

DISCUSSION

PAUL KLEMPERER: Cases of multiple polyposis are rated in the literature as very rare. Oberndorfer lists only about one hundred cases; it is interesting that we should have had the opportunity to observe three cases in recent years.

NICHOLAS ALTER: I think they are more common than reported. I had a few cases of extensive and diffuse polyposis at the Post-Graduate Hospital, and it was interesting that some of these polypi had a tendency to become malignant. Definite invasions were seen in multiple places. The condition is often associated with ulcerative colitis, and in many cases of the latter disease I have observed polyposis with hyperplasia, which may be the causative agent and the starting point of the condition. Probably ulcerative colitis has its foundation in inflammatory hyperplasia, followed by metaplasia and possible transformation into cancer.

PAUL KLEMPERER: Diffuse polyposis of the type illustrated in the first specimen is not to be identified with numerous polyps in the colon. It only seems as though it were merely a matter of quantitative difference. If the colon is riddled with polypi as in the case shown, it is different from the others in which one can easily count the number of polypi. As these cases are frequently observed in younger people, they have a pathogenesis different from the polyps that occur as a result of inflammatory processes after dysentery or ulcerative colitis. The fact that there is a considerable number of familial cases further shows that this type is different in origin from the type following colitis. The occurrence of such universal polyposis is very unusual, and I think one should not identify it with the occurrence of several polypi in the intestine, which is, of course, a very common experience.

NICHOLAS ALTER: I have had specimens, one in particular, showing a very diffuse polyposis and cancer.

PAUL KLEMPERER: That shows that the experience of different persons varies.

ADAMANTINOMA WITH METASTASIS TO THE LUNGS. DAVID PERLA and JEFFERSON VORZIMER.

An instance of adamantinoma of the jaw with metastasis to the lung is reported. The bronchi of the lower lobe were markedly dilated, and their lumina were filled with a cast of the tumor tissue. In places, the parenchyma was invaded. It is suggested that the tumor tissue was aspirated into the lung from the primary tumor via the trachea and bronchial tree and grew primarily within the lumina of the bronchi. No similar metastatic lesion in the lung in a case of adamantinoma was found in the literature.

THE DIOXYPHENYLALANINE REACTION IN GENERAL PATHOLOGY. GEORGE F. LAIDLAW.

The dioxyphenylalanine reaction is specific for two kinds of cells, myelogenous leukocytes and melanoblasts. The reacting cell turns gray or black on a colorless ground. The reaction is easily performed, constant and inexpensive.

With myelogenous leukocytes, the dioxyphenylalanine reaction duplicates the Schultze-Winkler reaction, but it has some advantages. The dioxyphenylalanine reagent keeps better, and in the dioxyphenylalanine reaction the granules of the leukocyte stain a fast black. They can be counterstained in any way desired and the section mounted in balsam, whereas sometimes it is difficult to preserve and mount Schultze-Winkler sections without destroying the preparation.

For melanoblasts, the dioxyphenylalanine reaction is the only reliable specific reaction. It cannot be replaced by silver, as claimed by Heudorfer, nor by dimethylphenylendiamine, as stated by Kreibich and by Meirowsky. Our experiments confirm those of Bloch and his school that silver and dimethylphenylendiamine stain melanin and melanin only. If melanoblasts happen to contain melanin, they will stain with silver or with dimethylphenylendiamine; if they do not contain melanin, silver and dimethylphenylendiamine leave them unstained, but they may still stain with dioxyphenylalanine.

Lantern slides of the dioxyphenylalanine reaction were exhibited, showing melanoblasts in normal Caucasian skin and in Negro skin, their increase in number in a skin that has been tanned by the x-rays, and their absence in vitiligo. Slides of pigmented moles showed the correspondence of the dioxyphenylalanine reaction with the production of melanin, being greatest just beneath the epidermis and fading out in the deeper layers of the mole. Slides of a pigmented Recklinghausen-Lappenelephantiasis from the sacral region showed an increase in the number of melanoblasts in the pigmented epidermis, together with groups of Mongol cells deep in the corium. The Mongol cells were active melanoblasts,

reacting both to dioxyphenylalanine and to silver. The subject was a Caucasian girl, 16 years of age. Section from other areas, such as the glutteal fold, in the same case of elephantiasis, showed no Mongol cells.

In association with Lester Cahn, the speaker reported the constant presence of melanin and melanoblasts in human gums, a fact heretofore unknown.

The conclusion is that the dioxyphenylalanine reaction is a valuable aid to the pathologist in the identification of myelogenous leukocytes; it is indispensable in the study of the production of melanin, both in benign and in malignant melanoma. As a specific stain for melanoblasts, the dioxyphenylalanine reaction identifies the true melanoblast in the metastases of melanoma and distinguishes it from mere phagocytes. However, in the identification of melanoblasts, it should be remembered that the melanoblast is dioxyphenylalanine-positive only when actively producing melanin, and that it does not produce melanin continuously. A positive reaction is reliable; a negative reaction has no significance.

A Simple Technic for the Dioxyphenylalanine Reaction. S. N. Blackberg.

The published technic of the dioxyphenylalanine reaction requires considerable chemical and technical skill. This has prevented its general adoption. My associates and I have succeeded in simplifying the technic so that it can be carried out easily and successfully in any laboratory.

The Stock Solution.—Dissolve 0.3 Gm. of dioxyphenylalanine in 300 cc. of distilled water, cork tightly and keep in the refrigerator. When kept cold, the solution remains unchanged for many weeks.

The Buffers.—Dissolve 11 Gm. of disodium hydrogen phosphate in 1,000 cc. of distilled water.

Dissolve 9 Gm. of potassium dihydrogen phosphate in 1,000 cc. of distilled water.

Buffer the solution to p_H 7.4 or 7.8 just before use. This can be secured with sufficient accuracy by mixing 50 cc. of the stock solution with 4 cc. of the potassium dihydrogen phosphate, and 12.5 cc. of the disodium hydrogen phosphate solution. The chief point is to have the p_H value above 7.3, below which the reaction does not take place. The p_H value may be 8.5 or even higher, giving a fast reaction.

The Sections.—Theoretically, frozen sections of fresh tissue should be used, but it is difficult to cut fresh tissue neatly. In practice, we follow Bloch's custom of hardening the tissue in 2 per cent formaldehyde for two or three hours. If fresh tissue is used, the sections are dropped from the knife directly into the buffered dioxyphenylalanine solution. Sections from formaldehyde-fixed tissue are rinsed in distilled water for five seconds or so and placed at once in the dioxyphenylalanine solution. Prolonged immersion in water is to be avoided, as it extracts the ferment rapidly.

The Reaction.—This takes place slowly at room temperature, and quickly at 56 C. It is usually conducted at 37 C. In about two hours the fluid turns reddish, then sepia brown. The first appearance of the sepia color marks the end of the reaction. A section is examined under the microscope. In a correct reaction, the melanoblasts and the leukocytes are gray or black, melanin retains its natural yellowish brown, and the collagen or other ground is colorless or pale gray. If it is desired to stain the leukocytes or melanoblasts more deeply, the section may be returned to the dioxyphenylalanine solution for another half hour or so.

Some tissues are sufficiently acid to lower the p_H value below 7.3, in which case the solution remains red, and the melanoblasts do not stain. When the tissue has been in formaldehyde, especially neutralized formaldehyde, the reaction is hastened, the fluid darkened and the ground often overstained. Since water cannot be used to wash out these disturbing elements, we change the dioxyphenylalanine solution for a fresh one after the first half hour, thus washing the sections with dioxyphenylalanine instead of water.

DISCUSSION ON PAPERS OF DR. LAIDLAW AND DR. BLACKBERG

S. M. PECK: After Bloch had demonstrated his dioxyphenylalanine reaction, his work could be divided into two phases, one, that in which he showed that the dioxyphenylalanine reaction is a ferment reaction which takes place only in the pigment-building cells at the time when formation of pigment is active, and two, that in which he showed that dioxyphenylalanine is probably the propigment. It is agreed among workers on pigments that the term melanoblasts refers to those cells that are pigment-builders, whether they are ectodermal or mesodermal in origin, and that the term chromatophores should be applied only to those pigment-containing cells that phagocytose melanin. The mesodermal melanoblasts in man are but rudimentarily developed, as in the blue nevus and in the mongolian spots; they are also found in the eye, particularly in the choroid. Bloch's claim that there is a distinct relationship between the pigment-building activity of the cell and the intensity of the dioxyphenylalanine reaction was amply substantiated by some work that I did. I was able to show that after thorium X was applied to the skin, the dioxyphenylalanine reaction became increasingly positive up to a maximum intensity in about five days, and then gradually returned to a normal level. It remains fairly intense for four weeks after the application of thorium X. This was the first step in the formation of pigment. Actual melanin was formed later, and at the time when the greatest amount of pigment was seen in the cells, the dioxyphenylalanine reaction was on the wane. I was able to show, furthermore, that embryologic formation of pigment took place along similar lines. The first step was the presence of dioxyphenylalanine-positive cells at the place where formation of pigment was to take place.

Dr. Laidlaw was correct, I believe, in attributing a phasic formation of pigment to the melanoblasts, and that may be the reason why in the intensely pigmented Negro skin one sees relatively few dioxyphenylalanine-positive cells, but perhaps the phase of formation of pigment is much more rapid in the Negro's skin than in the Caucasian's skin.

The question of the origin of the dendritic cells has been much discussed. My research on this subject has led me to conclude that there are three possibilities: first, that all melanoblasts have a dendritic shape, but that the dentrites are seen only when they contain pigment or oxydase; second, that the melanoblasts can have either a dendritic shape or the ordinary basal cell form, and third, that the dendritic cells represent changes in shape of the ordinary basal cells which take place during intense formation of pigment. My studies on the formation of pigment after the application of thorium X have led me to believe that perhaps the last is the true state of affairs. Early after the application of thorium X, a section stained with hematoxylin and eosin, or even with silver nitrate, showed very few dendritic cells per field. But with the dioxyphenylalanine reaction there were in a low power field as many as 20 cells showing dendrites. Later on as melanin was formed, the number of dendritic cells seen with the silver nitrate reaction closely approached the number seen in the earlier sections.

Bloch and I have developed a technic for demonstrating oxydase in the leukocytes which is much simpler and much more practical than the Schultze-Winkler reaction. Furthermore, since melanin is formed in this reaction, the fine granules can be accentuated by means of the silver nitrate. It must be borne in mind that the reaction in the leukocytes should not be confused with the dioxyphenylalanine reaction. The former is not specific and can be obtained with epinephrine and pyrogallic acid.

I believe that we now have additional proof in support of Bloch's claim that the dioxyphenylalanine reaction is a ferment reaction and is absolutely specific. In collaboration with Sobotka and Kahn at Mount Sinai Hospital, I was able to show that the dioxyphenylalanine oxydase reacts only with the levorotatory dioxyphenylalanine. The dextro compound, however, is acted on as well as the levo by the leukocytes. This goes hand in hand with what is known of other ferment reactions, and since the levorotatory compound is the natural one, it is a further corroboration that the levo dioxyphenylalanine is probably the propigment.

I believe that the specificity of the oxydase for the levo compound will help us in demonstrating metastases of melanoma. While in the hands of an expert the dioxyphenylalanine reaction can be easily differentiated from that of the leukocyte, there is often a great deal of difficulty because of poor frozen sections. Therefore I would suggest that when there is any doubt, a reaction with both levo and dextro dioxyphenylalanine should be done. If the reaction is negative with the dextro and positive with the levo, one is dealing with melanoblasts.

ABNER WOLF: I should like to say a word about the experience I had with the dioxyphenylalanine reaction. Dr. Laidlaw was kind enough to demonstrate the reaction to me. It proved to be very simple. I applied it in three cases of anterior poliomyelitis, as the question arose whether some of the cells of the exudate were microglia cells or polymorphonuclear leukocytes. With the aid of the dioxyphenylalanine reaction performed with the simplified technic of Drs. Blackberg and Laidlaw, this point was easily determined.

PAUL KLEMPERER: Did the monocytes give any reaction?

GEORGE F. LAIDLAW: No.

SPHEROIDAL CELL CARCINOMA (SEMINOMA) OF THE EPIDIDYMIS NOT INVOLVING THE TESTICLE. A. A. EISENBERG and HARRY WALLERSTEIN.

A man, aged 48, noted progressive swelling with some pain in the right testicle, over a period of one year. There was no history of trauma or of venereal disease. The testicle and epididymis, when removed, showed a large, solid epididymis, measuring 3.5 by 3 cm. It was enclosed in a thick fibrous capsule, which separated it from the testicle. On section, the cut surface of the epididymis was brownish and solid, and resembled fleshy carcinoma-like tissue. There was an occasional area of softening. The testicle was small and compressed, and showed no gross areas of involvement. Microscopically, the epididymis was entirely converted into neoplastic tissue consisting of large, pale cells, some round, and others polyhedral in form. There was a distinct uniformity in the type of cell, which had a clear cytoplasm with a large nucleus containing considerable chromatin material, and in many cases filling the entire cell. The cells were arranged in large masses with no tendency toward alveolar formation. A small amount of stroma was present, and this was infiltrated with lymphocytes. A few necrotic areas were seen. The testis was separated from the tumor by a thick band of fibrous tissue, and was compressed, with many atrophied tubules. Several sections failed to show neoplastic involvement, though, properly to exclude this, the whole specimen would have to be sectioned, which was not done.

A search of the literature revealed twenty reports covering twenty-three cases of primary malignant neoplasms of the epididymis. Of these only two were of the type reported by us. One case was reported by Hinman and Gibson, and the other, by Coleman, Mackie and Simpson.

We believe the term "spheroidal cell carcinoma" to be preferred to any other, because it avoids the controversy regarding the origin of this tumor that is caused by the use of the term "seminoma" by Chevassu and "embryonal carcinoma" by Ewing.

This report with the results of a thorough search of the literature have been sent for publication to *Surgery, Gynecology and Obstetrics.*

INTERSTITIAL HYPERTROPHIC NEURITIS. ABNER WOLF.

A housewife, aged 40, (Neurological Institute, service of Dr. Frederick Tilney), complained of pain in both arms and legs, great difficulty in walking and weakness of both hands. The illness began in 1914 with a callus across the sole of the left foot at the level of the metatarsophalangeal joint. In 1921 numbness developed in the region of the callus and extended to the toes. Gradual weakness of the toes appeared, and within a year they were completely paralyzed, and eventually markedly contracted. This caused pain across the instep on walking. At about

the same time, a similar process began in the left hand and progressed until there was contracture unaccompanied by pain, however. In 1928 the right foot and hand became involved. The patient's previous history and that of the family were without obvious bearing on the condition.

The patient showed generalized muscular wasting, most marked in the distal parts of the extremities; weakness of the intrinsic musculature of the hands and feet, with bilateral "main en griffe," contractures and pes cavo-equinovarus, and involvement of the flexors and extensors of the wrists and fingers and of the quadriceps extensor femoris and anterior tibial groups of muscles. The electrical reactions in the muscles of the right arm and leg indicated degeneration; such muscles as the biceps and tibialis anticus did not react to the faradic current. A number of the peripheral nerves were thick and easily palpable, notably the posterior auricular, median and ulnar of both upper extremities, both radials, the right perineal and posterior tibial, and both superficial perineal nerves. Deep pressure on the nerve trunks caused no pain. The head and trunk were normal. There were diminished appreciation of pain, temperature and touch of a glove, and the stocking type of distribution in all four extremities. Vibratory sensibility, as well as sense of position and movement, were much diminished in both feet. No astereognosis was noted. The fundi and the visual fields, the pupils, and the rest of the cranial nerves were normal. The intelligence was normal, with good memory and insight, and there was no speech defect.

On Dec. 15, 1930, a small portion of the posterior auricular nerve was excised. It was markedly thickened, measuring 4 mm. in diameter, and very firm. It was studied by means of cross-sections stained in various ways.

The epineurium, moderately and somewhat irregularly thickened, was composed of broad bands of collagen that became somewhat more delicate at its inner surface and were arranged in horizontally concentric layers. Some of the bands toward the outer edge were rather glistening and homogeneous, as if partially hyalinized. A considerable number of elongated, fibroblast nuclei lay between the fiber bundles, their long axes parallel to the concentric collagen bands. Those toward the outer surface of the epineurium were compressed, condensed and elongated, while of those toward its inner surface, many were more oval and vesicular.

The perineurium appeared myxomatous. Scattered, compact bundles of collagen running in the longitudinal direction were present in moderate numbers. Between these, and between them and both the epineurium and the endoneurium, was a loose, weblike mass of delicate fibers interlacing, in all directions and staining often indefinitely. These stained faint blue with Mallory's connective tissue stain, reddish in van Gieson's stain and faint tan with phosphotungstic acid-hematoxylin. On their surfaces, especially where they lacked definition, and in some of the spaces between them, was a finely granular material, faintly pink in hematoxylin-eosin, reddish with Mallory's connective tissue stain and faint gray in Laidlaw's silver stain for connective tissue. In Mayer's mucicarmine stain, no mucin was demonstrated, although occasionally some of the fine fibers took a reddish tinge. Lying in the strands of the loose web were a few fibroblasts. Most of them were rather elongated and had elongated nuclei with a little chromatin in coarse granules; a few were star-shaped, with nuclei more nearly spherical. The larger vasae nervorum in the perineurium showed moderate fibrosis. In many of them, the adventitia and most of the media seemed to have undergone the same myxomatous change as the perineurium. Many of the arterioles showed partial or complete hyalinization. There were a few scattered mononuclear leukocytes and lymphocytes in the perineurium.

The nerve bundles in this perineurial tissue were striking. In cross-section, they consisted of groups of spherical masses, each many times the diameter of an ordinary axon and its sheaths. These masses had a concentric, lamellated structure, looser toward the outer margin and compact internally. They were either empty or surrounded a myelin sheath and axon, or a naked axon. Each of these tubular structures showed from one to four longitudinally disposed nuclei,

varying in shape. Their chromatin was scanty and coarsely granular; they lay between the lamellae, and their structure was the same whether they lay abutting on the myelin sheath, on the internal surface of the ring, or toward the outer margin of the ring. Some investigators have referred to these formations seen in cross-section as "onion-bulbs," because of their concentric, lamellated structure.

The laminae took an intense stain for collagen. Toward the outer margin of the laminated structure, the laminae were often composed of contiguous, loosely arranged, longitudinal bundles of collagenous connective tissue. With the stains for reticulum, horizontal bands of reticulin could be seen in the same zone. This outer area of the lamellated structure likely represents a thickened band of endoneurium.

The inner laminae had greater circular continuity and were more compact. In most cases, they were directly continuous with the outer laminae, appeared collagenous and had the horizontal bands of reticulin. A few of the bulbs showed a more homogeneous central portion, clearly separated from the outer, thickened endoneurial layer. These homogeneous areas also took the collagen stain intensely, and with the immersion lens looked finely stippled, as if they had many fine longitudinal fibrils in their substance. The inner portions of the concentric, structures, it is likely, arose from hypertrophy and metamorphosis of the Schwann sheaths. The many nuclei seen in a single cross-section would represent an increase in the number of Schwann nuclei, since, ordinarily, only one such nucleus is present between two nodes of Ranvier.

The myelin sheaths were greatly reduced in number. No fragmentation of the myelin was encountered. In the preserved sheaths, the myelin was concentrated toward the margins of the sheath and about the incisors of Schmidt-Lantermann. With the Mallory connective tissue and Masson's trichrome stains, the neurokeratin network was well preserved in many of the undegenerated sheaths, and was stained orange and separated from the inner margins of the concentric, lamellated structures.

The total number of axons was increased, although many of the "onion bulbs" contained none. There was, however, a large number of naked axons of varying caliber, mostly delicate, lying eccentrically in the bulbs and at their margins, which represented regenerating nerve fibers as well as persisting sympathetic and demyelinated fibers. Of the persisting axons in a central position, some appeared hypertrophied, others, shrunken.

Thirty nine cases of interstitial hypertrophic neuritis have been described in the literature, with fourteen autopsies and five biopsies. An extended report is to appear soon in the *Bulletin of the Neurological Institute of New York*. We believe that this is a primary disease of the Schwann apparatus, characterized by overgrowth and sclerosis, and that the infiltrative cells in the perineurium are incidental to the degeneration of the myelin sheath and axons. Syphilis, intoxications, and other exogenous and endogenous factors have not appeared consistently enough in association with the disease to postulate them as the underlying cause. The frequent familial occurrence and onset in early youth suggest a congenital condition.

DISCUSSION

ALFRED PLAUT: Is anything known about the early stages of this disease?

ABNER WOLF: This condition does not come under observation until it is advanced. The changes in the Schwann cells are the initial ones; they do not produce any early symptoms because the myelin sheaths are intact for a long time, and the axons are the last to go, so that symptoms do not arise until late.

ALFRED PLAUT: Do you call this "neuritis" from the general clinical standpoint only — not from the anatomic standpoint?

ABNER WOLF: Yes.

LEON H. CORNWALL: I saw this case, and have seen three others. This is the first time that I have seen sections of this tissue stained by the Laidlaw

method. Dr. Wolf did not say whether or not he accepted the explanation in the literature, that this process is initiated by the Schwann cells and only later participated in by the epineurium, the endoneurium and the perineurium. It seems to me that there may be some doubt whether the so-called "onion bulbs" are comprised of Schwann cell components only. It is somewhat important to determine that. The same point arises in the conception of regeneration. Dr. Hassin of Chicago has advanced the opinion that the nuclei seen in nerves following injury, which have always been considered nuclei of Schwann cells, are derived from the mesodermal sheaths of the nerves and not from the ectodermal constituents. He believes that the Schwann cells act as scavengers in the peripheral nervous system in a manner similar to that exemplified by certain glial cells in the central nervous system, and that, when degeneration of myelin occurs, these scavenger cells ingest the degenerated lipoid products, transport them to the blood channels, and then end their existence. He believes that the cells forming the cordons between which the regenerating axis-cylinders insinuate themselves are of mesodermal origin. It may be that the pathologic change here is initiated by the mesodermal rather than by the ectodermal constituents. I would not imply that I hold that view, but I think it is possible, and I am rather interested to know Dr. Wolf's opinion of the significance of the fibrils that are stained by the Laidlaw method.

ABNER WOLF: I think Dr. Cornwall's point is well taken. However, the presence of reticulum between these bundles of Schwann cells does not rule out their being the primary factor in the formation of the lesions of the disease. Both Nagoette and P. Masson, among others, are of the opinion that the Schwann cells can produce both reticulum and collagen. Nagoette, in his work on regeneration in peripheral nerves, claimed that bands of Schwann cells growing out of the regenerating peripheral stump are able to lay down collagen in the absence of any fibroblasts. Fibroblasts, in his opinion, only secondarily invade the Schwann bands after the newly formed endoneurium has completely surrounded the reformed Schwann sheaths. Masson, in a report on schwannomas soon to appear, is of the opinion that the Schwann cells take part in the laying down of connective tissue fibers in these tumors. If these cells are capable of elaborating such fibers, the appearances seen in the Laidlaw stain in interstitial hypertrophic neuritis are not inconsistent with the Schwann cell hypothesis as to the formation of the typical lesions.

AORTICOVENTRICULAR FISTULA WITH ENGRAFTED ACUTE BACTERIAL ENDOCARDITIS. MENDEL JACOBI and ABRAHAM HEINRICH.

A white boy, 1½ years old (presented at the meeting on Dec. 10, 1931), was hospitalized because of pyrexia and painful knee and elbow joints. The heart was enlarged; apical and pulmonic systolic murmurs were present. A loud, harsh, to and fro murmur was present at the midsternum. The blood culture was positive for Streptococcus haemolyticus. The child died on the following day.

On necropsy, the heart showed a patch of fibrinous pericarditis over the left ventricle and over the conus. The aortic valve was bicuspid, and both coronary orifices opened into the larger anterior cusp. Between these two and on the same level, an opening 0.6 cm. in diameter led into a fistulous tract, which extended obliquely downward, forward and to the right, opening into the right ventricle beneath the commissure between the right and left posterior pulmonic valve cusps. The tract narrowed toward the ventricle and was filled with gray-yellow thrombus. A triangular cavity in the posterolateral right ventricular wall communicated with the tract. The kidneys presented minute cortical abscesses.

Microscopically, the tract was composed of a peripheral zone of granulation tissue and a lumen containing polymorphonuclear leukocytes, streptococci and débris. The medial zone of granulation tissue was widest at the ventricular end.

We explain the congenital defect as follows: The distal bulbar swellings that make up part of the aortopulmonic septum and are also the origin of the

aortic and pulmonic valve cusps are irregular as to form and occurrence, in man. We can conceive of a persistent communication in this distal bulbar septum itself, distal to the aortic valves, and the pulmonic valves arising immediately distal to such a defect. In support of this opinion, the pulmonic valves were 0.8 cm. above the aortic valves as measured from the apex. Usually the two valves are on the same level.

CHICAGO PATHOLOGICAL SOCIETY

Regular Monthly Meeting, April 11, 1932

R. H. JAFFÉ, *President, in the Chair*

IMPACTION OF A NEURO-EPITHELIAL CYST IN THE THIRD VENTRICLE OF THE BRAIN. CARL O. RINDER and PAUL R. CANNON.

A woman, aged 47, died as a result of the impaction of a cystic tumor in the foramen of Monro. The tumor was 15 mm. in diameter, was filled with translucent, gelatinous material and was attached to the right choroid plexus. The contents was lipochrome, and the lining epithelium was ciliated. Such tumors, usually described as "colloid cysts," are supposed to arise from the paraphysis.

The clinical symptoms extended over ten years. These were intermittent headaches, nausea, visual disturbances and sudden relief by changes of posture, owing, presumably, to a ball-valve action of the cyst. Finally, the cyst became impacted, and death occurred rapidly from acute internal hydrocephalus.

DISCUSSION

J. P. SIMMONDS: I have examined the brain of a patient whose symptoms duplicated those described. The convolutions of the brain were flattened, and there was a cyst of the choroid plexus.

A. A. ARKIN: Ecchinococcus cysts and cysticercus cysts of the choroid plexus deserve consideration.

G. W. HALL: The symptoms of patients with these cysts, though very characteristic, may resemble those of other conditions, such as migraine.

APPENDICITIS IN MEASLES. I. DAVIDSOHN and JACOB M. MORA.

The literature on the histologic changes in the tonsils and in the appendix in the prodromal stage of measles and during the course of the disease was reviewed. A second case was reported with characteristic giant cells in the lining of the appendix.

DISCUSSION

R. H. JAFFÉ: Similar cells occur in the secondary lesions of syphilis. These giant cells are not specific for any one condition.

EXPERIMENTAL FAT EMBOLISM OF THE MYOCARDIUM IN DOGS. S. A. SZUREK and Z. G. CZAJA.

The results of emboli of fat in the coronary arteries of dogs were reported, with a brief survey of the literature on fat embolism. Oil pressed out from adipose tissue of dogs was slowly injected into one or more divisions of the anterior branch of the left coronary artery, and the hearts were examined after intervals of from six hours to thirty days. Instead of localized obstruction at some place near the mouth of the pulmonary artery in the aorta, as occurs with spontaneous occlusion in the human heart, now so familiar to clinicians, the

obstruction in the hearts of these dogs was due to a fluid embolus, spreading widely in the capillary bed distal to the site of injection. This factor resulted in some differences between the infarcts produced and those made experimentally in other ways and studied by other observers. The adventitious fat and the changes connected with its ultimate disposal in the entire region infarcted were observed; phagocytosis of fat and of the detritus of blood and necrotic muscle were conspicuous, and it was also noted that some of the oil introduced was still present in the partly healed lesions as long as thirty days after its introduction.

After this study was finished in the spring of 1931, and a report prepared for publication, an article by Vance appeared, (The Significance of Fat Embolism, *Arch. Surg.* **23**:426, 1931). The streaky and "flamelike" hemorrhages that he found in the myocardium of human hearts caused by emboli of fat following injuries accompanied by fractured bones are of interest because similar hemorrhages were observed in the dogs' hearts. The comment made by Vance on an absence of reports of human fibrous myocarditis due to fat embolism is also pertinent to this study of experimental lesions, for in the dogs' hearts scars were formed.

STENOSIS OF THE SUPERIOR VENA CAVA DUE TO MEDIASTINAL TUBERCULOSIS. GEORGE MILLES.

Obstruction of the superior vena cava may arise from aneurysms, mediastinal growths of many kinds, enlarged lymph nodes and thrombosis. Edema and cyanosis of the head, neck and thorax to the level of the fourth or the sixth ribs are the important clinical symptoms. The edema is most conspicuous in the head and neck, and least so in the arms. The veins of the collateral circulation are prominent. The subjective symptoms are dyspnea, orthopnea, dizziness, fulness of the head and somnolence.

A white man, 42 years of age, an ex-prize-fighter, was first seen on Feb. 5, 1931. He complained of dizziness, dyspnea, orthopnea, swelling of the face and neck and sleepiness. He had been well until the summer of 1930, when he noted dyspnea on exertion, dizziness, orthopnea and drowsiness. At about the same time, his face and neck began to swell, and his collar size increased. The symptoms were slowly progressive, accentuated on exertion or stooping, and during the following months the swelling of the face and neck fluctuated in degree, depending on his physical activity. About December, 1930, choking spells and extreme orthopnea disturbed him at night, and watering of the eyes became almost constant. During this time he had a slight, rather insignificant cough and lost about 6 pounds (2.7 Kg.). Physically, he was well nourished and exceptionally well developed, of the short, stocky type. His face and neck were definitely edematous and dusky; his lips were slightly cyanotic, and the conjunctivae showed injection and were edematous. The jugular veins were distended, and prominent varices encircled the costal margins. Slight widening of the upper mediastinal dulness was noted on percussion. The blood pressure was 128 systolic and 78 diastolic in both arms. Laboratory examination revealed 10.5 Gm. of hemoglobin per hundred cubic centimeters of blood, 4,560,000 red cells and 5,350 white cells of which 40 per cent were lymphocytes. The results of the Wassermann and Kahn tests were negative. The blood chemistry and the urine were normal. The x-ray plates and fluoroscopic examination revealed a slightly widened upper mediastinal shadow, which was interpreted as a tumor; no evidence of aneurysm was found. Deep x-ray therapy caused no change in the clinical findings during the following months. However, the hemoglobin increased to 16.5 Gm. per hundred cubic centimeters of blood and the red count to 5,480,000. The patient was observed until November, 1931; then he began to complain of some increase in dyspnea, although objectively little change had occurred. The cause of the obstruction was thought to be a benign tumor, and in view of the hopeless outlook a mediastinal exploration was undertaken by Dr. Lindon Seed. Markedly dilated superficial veins were encountered when the skin was incised. The right internal mammary vein was about 8 mm. in diameter, and when it was opened, a stream

of blood spurted 20 cm. from the upper end. The mediastinum was widely exposed, but no tumor was found. The superior vena cava was distended, blue and thick-walled. The wound was closed. On the following day, the edema of the head and neck increased, the arms were edematous, and cyanosis and dyspnea were marked. Respirations became rapidly labored, the edema and cyanosis more pronounced and the patient died on the second day after operation.

Postmortem examination demonstrated marked dilatation of the superficial veins and of the internal mammary, azygous and superior epigastric veins. A cartilagenous, poorly defined mediastinal mass adherent to the lung encircled the superior vena cava about 4 cm. above the right auricle. The lumen in this region was 2 mm. in diameter; the wall was thickened to 7 mm. by dense connective tissue, and at the center of the encircling mass was cheesy necrotic material like a necrotic lymph gland. Above the stenosis, the blood vessel was dilated moderately. The other viscera had no changes.

Microscopic sections through the stenosis demonstrated a central region of caseation necrosis. About this was dense hyalinized connective tissue with diffuse and focal infiltrations by lymphoid and epithelioid cells, fibroblasts, a few Langhans giant cells and macrophages. No tubercle bacilli were found in sections stained by the Ziehl-Nielsen method. However, macrophages containing a few variable-sized, acid-fast granules were noted. A diagnosis of chronic fibrocaseous tuberculosis of a mediastinal lymph gland was made. The stenosis of the superior vena cava was caused by the scar tissues around a caseous, tuberculous mediastinal lymph gland.

BUFFALO SOCIETY OF PATHOLOGISTS

Meeting of April 26, 1932

KORNEL TERPLAN, *President, in the Chair*

PNEUMONIC CHANGES IN A FIVE MONTHS' FETUS. MARGARET WARWICK.

The mother of the infant had an entirely normal pregnancy, with no infection of any kind. Labor was spontaneous, and she delivered herself of a male fetus, weighing 13 ounces (404.3 Gm.), and, according to her last menstrual period, of a little less than five months' gestation. This fetus apparently had been dead for a short time before birth, but showed nothing of interest on gross examination. Microscopic sections showed the only pathologic lesions present to be in the lung. Only bronchiolar structures corresponding to the primitive alveoli were present. In all these, forming together a glandlike alveolar structure, were large collections of pus cells, in some of which could be made out a few brownish granules. The tissue between the primitive alveoli showed very mild infiltration by pus cells. Gram stains made on the pulmonary tissue failed to demonstrate any bacteria. This is a case illustrating pneumonic changes in a five months' fetal lung apparently caused by aspiration of amniotic fluid, in which there may have been some meconium as shown by brownish granules in the pus cells. The mother made an uneventful recovery with no evidence of any inflammatory process. Control examinations on sections taken from lungs of the same fetal age did not show the findings described.

CONGENITAL ENDOCARDIAL AND MYOCARDIAL FIBROSIS WITH CALCIFICATION. W. F. JACOBS.

The case was that of a new-born girl who survived birth approximately four hours; she was cyanotic at first and continued thus until death. Gestation and delivery were normal. There seemed to be, however, an excess of amniotic fluid.

The postmortem observations were typically those of chronic passive congestion. The heart was much enlarged. This enlargement was symmetrical, involving the ventricles only. The shape of the heart was distinctly bulbous. The walls were resilient, so that the organ was not unlike a thin-walled rubber ball that after invagination springs back into shape. Both ventricles were dilated; the walls were about 5 mm. thick. The endocardial surfaces of both ventricles showed diffuse fibrosis, and on the cut edges fibrous strands could be seen penetrating the muscle. There was an open foramen ovale, normal in outline, and a patent ductus arteriosus of normal length and width. Histologically, the endocardium showed diffuse fibrosis. Areas of fibrosis and calcific deposits were found in the muscle. No cellular infiltration indicating an inflammatory process was seen.

The endocardial fibrosis can be assumed to have developed on a mechanical basis, as described by Marie Hertel in cases of so-called "functional elastic parietal endocardial fibrosis." This endocardial fibrosis may be secondary to the changes demonstrated in the muscle. The cause of the muscle damage could not be determined. B. Fisher reported a case in which there were endocardial and myocardial lesions similar to this one. In his case, however, infiltration by white blood cells was seen, and the mitral valve showed also fibrous lesions.

Bacillus Friedlander Septicemia. E. T. Mueller.

A white man, 63 years old, was in good health until Feb. 21, 1932, when he had a severe chill lasting thirty minutes. After that he felt well until the middle of March when he again had chills, which came on almost daily. Physical examination revealed only enlarged cardiac dulness. Moderate leukocytosis was present. Blood specimens taken on several occasions gave pure cultures of Friedländer's bacillus. At autopsy, no evidence of pneumonia or pleuritis was found. There was a large abscess below the left diaphragm, together with septic infarctions of the spleen. Other abscesses were found in the pancreas and the prostate. Purulent leptomeningitis was also present, and septic emboli were discovered in slides from the myocardium. Smears and cultures taken from the pancreas, the prostate and the meninges yielded only Friedländer's bacillus.

Cystitis Emphysematosa in a Diabetic Patient. S. Sanes.

Necropsy revealed cystitis emphysematosa in a 62 year old, white woman. Other important findings included marked generalized arteriosclerotic changes, especially of the basilar and vertebral arteries, with calcification and narrowing of the lumen; focal malacia of the pons with gliosis, and marked atrophy of the pancreas. During life the patient showed frequency of urination. The blood sugar was 790 mg. per hundred cubic centimeters; the carbon dioxide-combining power, 28 mm. of mercury. Grossly, the bladder was distended with 400 cc. of smoky yellow, gas-containing urine. Its entire lining was covered with white, foamy gas vesicles of varying sizes. Marked hemorrhage was also present. The histologic picture corresponded to chronic recurring cystitis with marked inflammatory edema, infiltration by round cells, many eosinophils, plasma cells and polymorphonuclear leukocytes, extensive recent hemorrhage, and pronounced desquamation of epithelium. Foreign body giant cells and endothelial giant cells were also noted. Throughout all layers of the wall were gas cysts, which included distended lymphatic vessels and emphysematous tissue spaces. Smears from the surface of the bladder and from the gas vesicles showed only gram-negative, plump bacilli with rounded ends. A culture of Escherichia vesiculoformis was obtained from the urine. Cultures from the bladder, taken after the organ had been fixed, were negative. Bacterial stains revealed short, rounded bacilli in the tissues. Factors of etiologic and pathogenic significance in this case, including sex, chronic invalidism, distention of the bladder with residual urine, cystitis, bacteria and hyperglycema, were stressed. Twenty-nine instances of cystitis emphysematosa in human beings and animals have been reported. Two of these cases occurred in diabetic subjects.

HODGKIN'S DISEASE OF THE BREAST. K. TERPLAN.

A Jewish woman, 58 years of age, entered the hospital complaining of a lump and pain in the right nipple. The lump had been present for a year, growing gradually larger and involving the areola. The past history was negative. Physical examination revealed a small, hard, solitary node on the right side of the neck. The right breast showed an enlarged, deformed nipple with a lumpy involvement of the pigmented area about the nipple. Nodes were palpable both in the axillae and in the groins. They were soft, movable and bean-sized. In the hospital a radical amputation of the right breast was performed, with removal of the axillary nodes. Important laboratory findings included a red blood count of 5,120,000, 80 per cent hemoglobin, and a white count of 9,450, with an increased number of eosinophils, basophils and monocytes. The Wassermann reaction was negative.

Grossly, the breast showed an elongated and deformed nipple, which was firm and dark brown. The areola was dark brown. The skin was not desquamated, but irregular. On section, the tissue underneath the nipple and areola, surrounding the ducts, was grayish white, firm and nodular. The remaining mammary tissue appeared normal. The lymph nodes were small, bean-sized, not hard, and on section glistening gray. The histologic picture showed a typical Hodgkin's granuloma around the ducts. In one axillary lymph node was noted a small nodule in beginning fibrosis with changes typically those of Hodgkin's disease.

The literature disclosed only one report of Hodgkin's disease of the breast, that of a case in a 16 year old girl with involvement of several peripheral lymph nodes, described by Kuekens.

The carcinoma-like gross picture of Hodgkin's disease of the breast, resembling somewhat superficial carcinoma of the ducts (so-called Paget's disease), was pointed out. The question of the pathogenesis of the changes in the breast was discussed, and the origin in this case by way of a retrograde lymphogenous spread in connection with the changes found in the axillary lymph nodes was considered.

CHANGES IN THE BRAIN IN A CASE OF FATAL INSULIN SHOCK. K. TERPLAN.

A diabetic, white boy, 16 years old, had been given, at home and in the hospital, 92 units of insulin within twenty hours for apparent diabetic coma. Following this, he showed severe generalized convulsions, tonic and clonic, with nystagmus and twitching of the right side of the face and of the tongue. The blood dextrose was 46 mg. per hundred cubic centimeters; the white blood count was 12,000, with 81 per cent polymorphonuclear cells; the temperature was 101 to 107 F. After treatment to combat the hypoglycemia had been carried out, the blood sugar rose to 190 and 162 mg. per hundred cubic centimeters. The patient, however, never regained consciousness, dying in three days.

The most important postmortem observation was that of extreme edema of the brain (weight, 1,535 Gm.) with marked injection of the veins in the distended leptomeninges and in the brain substance itself. The same swelling was also noted in the spinal cord, which was closely pressed to the pachymeninges. The subdural space was practically obliterated, and the ventricles were markedly diminished in size, compressed by the swollen brain substance. Almost no spinal fluid was present. The pancreas weighed 34 Gm.

Sections stained by Nissl's method showed very severe changes in different parts of the cortex, chiefly in the occipital and frontal lobes, the island of Reil and the hippocampal gyrus. The changes consisted of extensive colliquation of the ganglion cells (many pictures of so-called Nissl's *Zellveränderung* being present), especially in the third layer. In some places, this layer had almost entirely disappeared. The glia cells presented severe regressive changes of the so-called ameboid type; the capillaries showed extensive swelling of the endothelial cells. The changes were specially present in the depths of the gyri. The motor region showed almost no destruction compared with the other cortical areas. The ganglion cells in the brain stem, medulla, spinal cord and basal ganglions were also much less damaged. The etiologic factors involved in the severe destruction

of the ganglion cells in hypoglycemic conditions, particularly the marked edema of the brain, were discussed. The literature was reviewed and only one similar observation—two cases by Wohlwill—was found. In Wohlwill's cases, however, the histologic changes were more diffuse, and, strangely enough, no edema was present. My case demonstrated most clearly the reciprocal relationship between true swelling of the brain and the amount of cerebrospinal fluid. Several antemortem attempts to obtain spinal fluid by lumbar and cisternal puncture were fruitless. Only a small amount of bloody fluid was procured—no real spinal fluid.

DISCUSSION

BYRON D. BOWEN: This patient's symptoms were unquestionably due to insulin shock produced by the injection of a large quantity of insulin when the patient was already having hypoglycemic symptoms brought on by exercise. Adequate treatment was not given until eighteen hours after the onset of symptoms. The restoration of the hypernormal glycemia together with a sedative controlled the convulsions, but did not restore consciousness. These points suggest that the changes in the brain produced by hypoglycemia may reach a point that is irreversible by dextrose.

Book Reviews

Man and Medicine: An Introduction to Medical Knowledge. By Dr. Henry E. Sigerist, Professor at the University of Leipzig. Introduction by Dr. William H. Welch, Professor of the History of Medicine, the Johns Hopkins University. Translated by Margaret Galt Boise. Cloth. Price, $4. Pp. 340. New York: W. W. Norton & Company, Inc., 1932.

The original German edition was published by Georg Thieme in Leipzig in 1931 under the title "Einführung in die Medizin." The following review was printed in the ARCHIVES (**12**:519 [Sept.] 1931):

"The author is Sudhoff's successor as professor of medical history in the University of Leipzig. He addresses himself especially to young persons about to begin the study of medicine. His object is to give them needed insight into the task ahead of them by means of a simple, yet comprehensive, conspectus of medicine as a whole on a historical or a developmental basis. There are seven chapters. The first deals with the structure and function — anatomy, physiology and psychology — of normal man. The necessity for the physician to acquire a broad knowledge of man in all his relationships is stressed. The next four chapters discuss the patient and disease. The growth of the concept of disease, its course and causes are discussed with admirable clearness. Then there is a chapter on diagnosis, healing and prevention. The last chapter is devoted to the doctor himself and his relation to society. The book is written in a remarkably clear, direct and effective style. Typographically, the failure to indent the paragraphs may be confusing to the reader. The book is highly interesting and will be of great help to medical students at the beginning of their course. It is recommended to all who are interested in the development of medicine and especially to medical educators. Sigerist shows clearly that as the developmental relations of various subjects in the study of medicine come to be understood, the sense of discontinuity in the medical curriculum, especially in the first two or three years, tends to vanish. The book merits translation into English."

Not much needs to be added to this statement. Dr. Welch, in his foreword, emphasizes that the clear and flowing style has been well preserved in the translation by Miss Boise. The book has been translated into Swedish, and translations into French and Spanish are to follow. The author writes in his preface: "The books is . . . a first attempt to picture the whole structure of medicine in the frame of general culture. When it appeared in Germany a year ago I was pleasantly surprised to find that it was welcomed by a large public outside of medical circles. Now a visit to Baltimore . . . and a lecture tour through the United States, have impressed me with the fact that there is in America a similar interest in the cultural aspects of medicine. I am therefore encouraged to believe that the present translation will appeal to the laity, as well as to medical students and physicians, in the English-speaking world." Simultaneously with the appearance of this translation comes the announcement that the author has accepted the professorship of the history of medicine in the Johns Hopkins University on the retirement of William H. Welch.

Human Cancer: Etiological Factors; Precancerous Lesions; Growth; Spread; Symptoms; Diagnosis; Prognosis; Principles of Treatment. By Arthur Purdy Stout, M.D., Associate Professor of Surgery, College of Physicians and Surgeons, Columbia University; Attending Surgical Pathologist, Presbyterian Hospital, New York. Cloth. Price, $10, net. Pp. 1007, with 331 original engravings. Philadelphia: Lea & Febiger, 1932.

The opening sentence of the preface reads: "This monograph, as its subtitle indicates, is an attempt to discuss the development and growth of all the different kinds of cancer in the human body. It has long been recognized that each

particular anatomical region of the body produces cancers which differ in many respects from those in other parts of the body. Therefore, this book deals with cancer by regions." However, tumors of the central nervous system, malignant or benign, primary or secondary, are not considered except mainly for brief references to Hodgkin's disease, leukemia and lymphosarcoma of the brain and spinal cord. The title of the book does not indicate the omission, and no mention is made of it in the preface.

The word cancer is used to include every type of malignant tumor. In order to avoid confusion, only those names of different tumors are used "which are current, most widely known and therefore recognized by the greatest number." This is a good rule for a book like the one under consideration, but to apply the word epithelioma as the only designation to practically every form of carcinoma arising in flat surface epithelium is not in accord with the best usage, at least by pathologists, and furthermore is undesirable because it tends to create a suspicion that somehow epithelioma differs radically from carcinoma. In the index of the book, squamous cell carcinoma of the breast, the bronchus, the conjunctiva, the larynx, the lip, the tongue, the urethra, the skin, and so on is not listed under carcinoma but under epithelioma, while under skin, larynx and the like, carcinoma is not given, but squamous cell epithelioma. This arrangement is awkward. The simplest way would have been to have used carcinoma as the standard term for all carcinomatous cancers.

After a general introduction of four pages come forty-seven chapters on cancers in various parts of the body except, as stated, the central nervous system. In general, the chapters follow this order: introduction; etiologic factors and precancerous lesions; the beginning, growth and spread of the cancers under consideration; the symptoms and signs, and the essential principles of treatment. There are 331 original illustrations of gross and microscopic appearances, almost all photographic (not engravings), and for the most part commendable. The value of certain photomicrographs of appearances under higher powers, magnification not stated, is questionable. The presentation is clear and orderly. The book contains in well organized form a large amount of reliable information about the various types of cancer in different parts of the body exclusive of the central nervous system.

The Life of Edward Jenner, M.D., F.R.S., Naturalist and Discoverer of Vaccination. By F. Dawtrey Drewitt, M.A., M.D., F.R.C.P. Cloth. Price, $2. Pp. 127, with portrait. New York: Longmans, Green & Company, 1931.

And he stood between the dead and the living; and the pestilence was stayed.—Numbers XVI, 48.

Much has been written about Edward Jenner, mostly in the form of brief sketches in medical journals. The value of his work to humanity is recognized: he is one of its greatest benefactors. Of the formal biographies of Jenner, there has been only one, John Baron's, published in two volumes (1827-1838), the last fifteen years after Jenner's death, in which the "true and genuine lineaments of his mind should stand forth in all their fair and just proportions." Fortunately the records in Baron's work are an invaluable source of information about Jenner —true "memoirs pour service"—but obviously they themselves will be read by only a few. Drewitt's little book, which is based mainly on Baron's, gives an excellent short account of Jenner's life which should interest wide circles of readers. In short space the author succeeds in giving an accurate, comprehensive and winning picture of Jenner: his life as a country doctor, his observations in natural history, his establishment by simple experiments of vaccination against smallpox and his wisdom, simplicity and benevolence.

Die theoretischen Grundlagen und die praktische Verwendbarkeit der gerichtlich-medizinischen Alkoholbestimmung. Von Prof. Dr. E. M. P. Widmark, Mediz.-chem. Institut der Universität Lund, Schweden. Neue Folge, Helt 11. Fortschritte der naturwissenschaftlichen Forschung. Herausgegeben von Prof. Dr. Emil Abderhalden. Paper. Price, 14 marks. Pp. 140, with 59 illustrations. Berlin: Urban & Schwarzenberg, 1932.

A practical and reliable micromethod for determining the presence of ethyl alcohol in the blood is described, based on the bichromate method. The micromethod has been used extensively in Sweden to determine alcohol in the blood for medicolegal purposes. The results of examinations of about seven hundred samples of blood in the course of routine investigation of traffic accidents are presented and discussed. Especially interesting cases are reported in detail. The determination of alcohol in the blood and urine in necropsies is also considered. The book is a highly important contribution to the study, scientific and practical, of the medicolegal problems of alcohol.

General Bacteriology. By Edwin O. Jordan, Ph.D., Professor of Bacteriology in the University of Chicago, and the Rush Medical College, Chicago. Tenth edition, entirely reset. Cloth. Price, $6 net. Pp. 819, with 200 illustrations. Philadelphia: W. B. Saunders Company, 1931.

Not much need be said by way of introducing the tenth edition of this standard and popular textbook. The revision has brought the book well abreast with current knowledge. Variation, undulant fever, filtrable virus diseases and bacteriophage are some of the topics that have received special consideration. The question of "nomenclature has been dealt with perhaps rather summarily," says the preface. "Generic names that have come into quite general use, such as Salmonella, Mycobacterium and Brucella, are tentatively employed, and even Eberthella has been somewhat reluctantly introduced. Convenience rather than strict rules of taxonomy seems likely to govern the naming of bacteria until a general nomenclatural system can be worked out by international agreement." Although the number of pages now is 819, this increase does not indicate any relaxation in the concise clearness, the judicial restraint and the remarkable accuracy of the presentation. In these respects the book continues to be a model.

Books Received

COLLECTED REPRINTS FROM THE LABORATORIES OF THE MOUNT SINAI HOSPITAL, NEW YORK. By Louis Gross, M.D., Director, 1931.

MEDICAL ASPECTS OF OLD AGE. BEING A REVISED AND ENLARGED EDITION OF THE LINACRE LECTURE, 1922. By Sir Humphrey Rolleston, Bart., G.V.C.O., K.C.B., M.D., Hon. D.Sc., D.C.L., LL.D., Regius Professor of Physic in the University of Cambridge, Physician-in-Ordinary to the King, Sometime President of the Royal College of Physicians of London. Price, $3. Pp. 205. New York: The Macmillan Company, 1932.

MAN AND MEDICINE: AN INTRODUCTION TO MEDICAL KNOWLEDGE. By Dr. Henry E. Sigerist, Professor at the University of Leipzig. Introduction by Dr. William H. Welch, Professor of the History of Medicine, the Johns Hopkins University. Translated by Margaret Galt Boise. Price, cloth, $4. Pp. 340. New York: W. W. Norton & Company, Inc., 1932.

HUMAN CANCER: ETIOLOGICAL FACTORS; PRECANCEROUS LESIONS; GROWTH; SPREAD; SYMPTOMS; DIAGNOSIS; PROGNOSIS; PRINCIPLES OF TREATMENT. By Arthur Purdy Stout, M.D., Associate Professor of Surgery, College of Physicians and Surgeons, Columbia University; Attending Surgical Pathologist, Presbyterian Hospital, New York City. Price, cloth, $10, net. Pp. 1,007, with 331 original engravings. Philadelphia: Lea & Febiger, 1932.

STUDIES IN NUTRITION: AN INQUIRY INTO THE DIET OF FAMILIES IN CARDIFF AND READING. By E. P. Cathcart and A. M. T. Murray, assisted by M. Shanks. Medical Research Council, Special Report Series, no. 165. Price, 6 pence, net. Pp. 28. London: His Majesty's Stationery Office, 1932.

LA MALADIE DE BOECK. SARCOIDES CUTANÉES BÉNIGNES MULTIPLES. Par le Docteur A. Kissmeyer, Médecin de L'Institut Finsen. Préface du Dr. J. Darier. Pp. 147, avec 67 illustrations et planches. Paris: Masson et Cie, 1932.

REPORT OF THE NEW YORK STATE VETERINARY COLLEGE AT CORNELL UNIVERSITY FOR THE YEAR 1930-1931. Legislative Document (1932) no. 19. Pp. 226. New York: Burland Printing Company, Inc., 1932.

VACCINATION PRÉVENTIVE DE LA TUBERCULOSE DE L'HOMME ET DES ANIMAUX PAR LE BCG. Rapports et documents provenant des divers pays (La France exceptée). Transmis à L'Institut Pasteur en 1932. Par A. Calmette et al. Pp. 366. Paris: Masson et Cie, 1932.